Draw Pharmacology in your mind

Autonomic Nervous System

If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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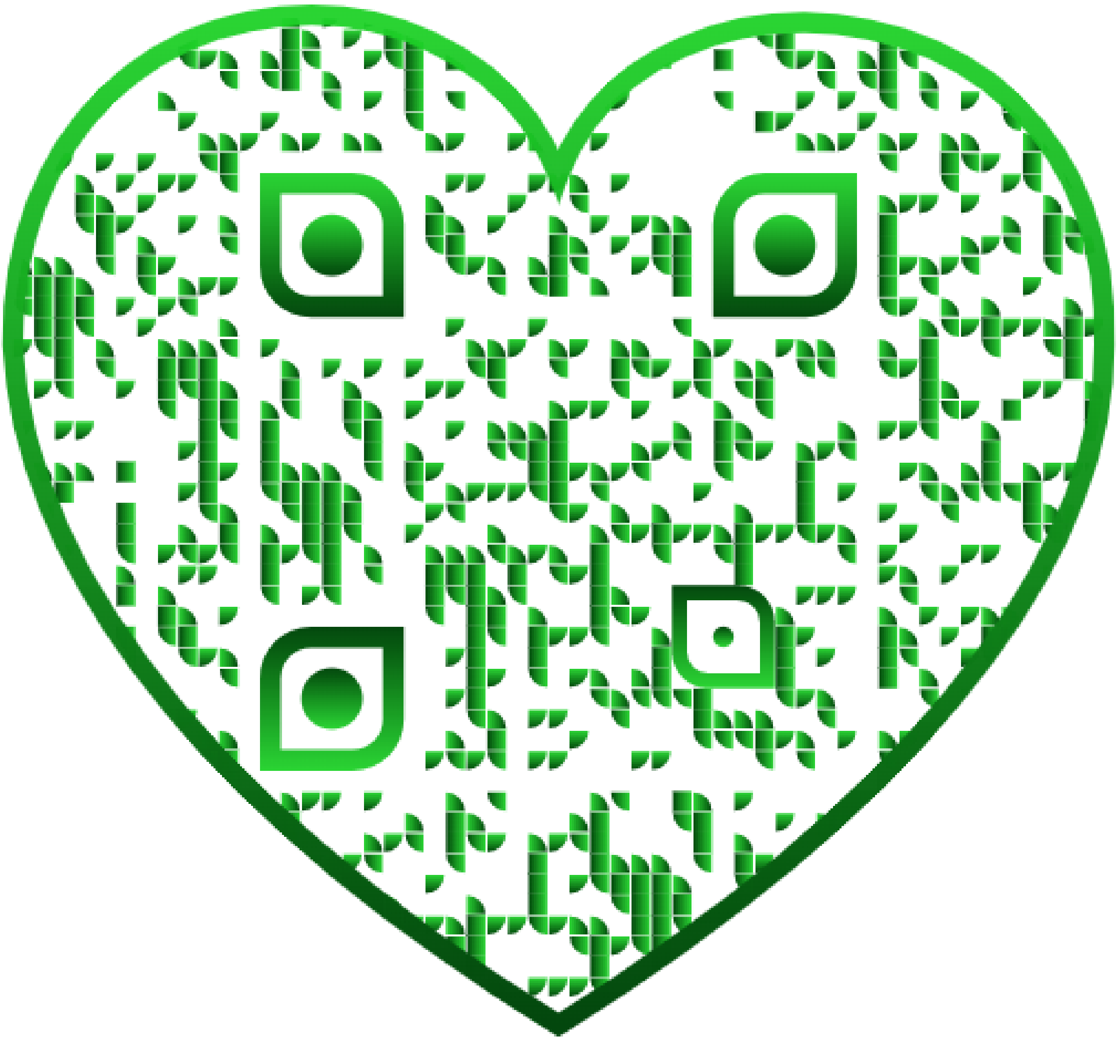
لا تنسونى من صالح دعائكم

Pharmacist. Alaa Nasr د. آلاء نصر



NERVOUS SYSTEM

Central nervous system (CNS)
- **Brain**
- **Spinal cord**

Peripheral nervous system (PNS)
- **Afferent neurons** — Originate from the organ (**ex.** skin) → to the CNS
- **Efferent neurons** — Originate from the CNS → to the effector organ (**ex.** muscles)

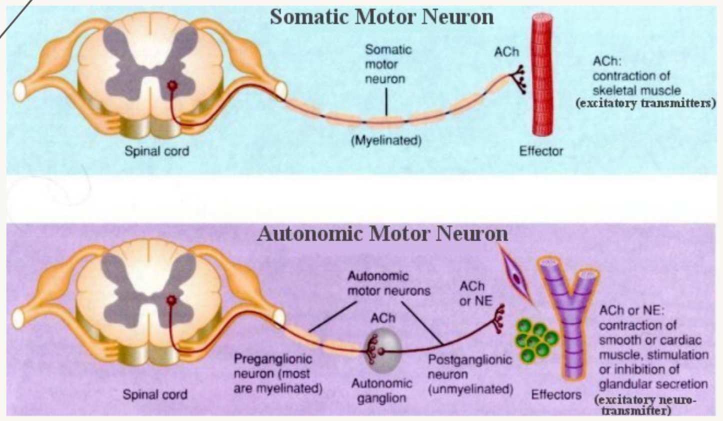
Somatic nerves

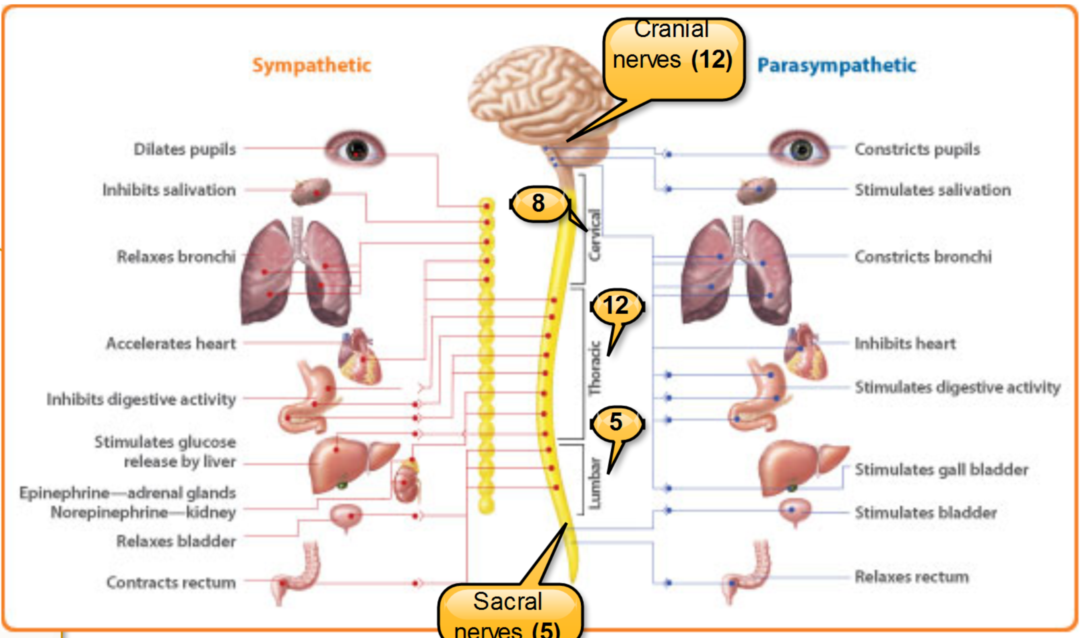
- Responsible for voluntary activity **ex.** skeletal muscle contraction
- **Supplies** skeletal muscles
- **NOT interrupted by ganglia**
- **Cutting a somatic nerve** → causes **paralysis**
- **Myleinated** (covered with mylein sheath)

Autonomic nerves

Autonomic Nervous System (ANS)

- Responsible for involuntary control **(unconsciously done)**
- **Supplies**
  - Smooth muscles (GIT - Bronchi - Bladder - Eyes)
  - Heart
  - Exocrine glands
- **Interrupted by ganglia**
- **Cutting an autonomic nerve** → **NO paralysis** → as ganglia can function automatically
- Postganglionic fibers are usually **NOT myleinated**


Somatic Motor Neuron
Somatic motor neuron
ACh
ACh: contraction of skeletal muscle (excitatory transmitters)
Spinal cord
(Myelinated)
Effector
Autonomic Motor Neuron
Autonomic motor neurons
ACh
ACh or NE
ACh or NE: contraction of smooth or cardiac muscle, stimulation or inhibition of glandular secretion (excitatory neuro-transmitter)
Spinal cord
Preganglionic neuron (most are myelinated)
Autonomic ganglion
Postganglionic neuron (unmyelinated)
Effectors


Sympathetic
Parasympathetic
Cranial nerves (12)
8
12
5
Sacral nerves (5)
Cervical
Thoracic
Lumbar
Dilates pupils
Inhibits salivation
Relaxes bronchi
Accelerates heart
Inhibits digestive activity
Stimulates glucose release by liver
Epinephrine—adrenal glands
Norepinephrine—kidney
Relaxes bladder
Contracts rectum
Constricts pupils
Stimulates salivation
Constricts bronchi
Inhibits heart
Stimulates digestive activity
Stimulates gall bladder
Stimulates bladder
Relaxes rectum

Cranial nerves are 12 pairs → III , VII , IX , X of them are *parasympathetic*

- III → **Oculomotor nerve** → Supplies iris and ciliary muscle in the eye
- VII → **Facial nerve** → Supplies salivary glands and lacrimal glands
- IX → **Glossopharyngeal nerve** → Supplies salivary glands , tongue and pharynx
- X → **Vagus nerve** → Supplies heart , lung and upper GIT
- **S** $_{2,3,4}$ → Supply lower GIT , urinary bladder and genitalia

Anatomy of the ANS

Preganglonic and post ganglionic neurons

The ANS carries nerve impulses from CNS → to the effector organ by ***two*** *efferent neurons:*

Preganglionic neuron

Its cell body is embedded in CNS (Brain , Spinal cord) → ends at the ganglion

Postganglionic neuron

Its cell body originates from the ganglion → and ends at the effector organ (**ex.** smooth muscles)

Ganglion is → the ***junction*** between the preganglionic and postganglionic neurons

Synapse → the ***junction*** between the *"preganglionic and postganglionic neurons"* **or between** a *"nerve and effector organ"*

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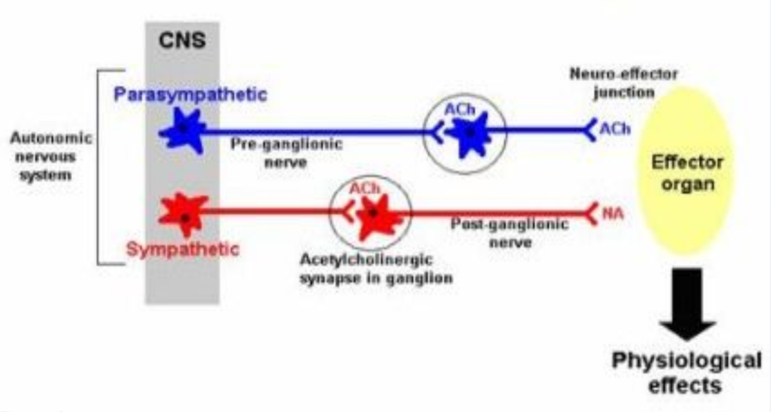
Devisions of ANS

Craniosacral — **Parasympathetic nervous system**
- Cranial nerves III , VII , IX , X
- Sacral nerves **S** $_{2,3,4}$

Thoracolumbar — **Sympathetic nervous system**
- **All** thoracic nerves **T** $_{1\rightarrow 12}$
- Lumbar nerves **L** $_{1,2,3}$


CNS
Autonomic nervous system
Parasympathetic
Sympathetic
Pre-ganglionic nerve
ACh
ACh
Acetylcholinergic synapse in ganglion
Neuro-effector junction
ACh
NA
Post-ganglionic nerve
Effector organ
Physiological effects

Preganglionic neuron	Long	Short
Ganglion	Near to or embedded at effector organ	Near the spinal cord in the form of sympathetic chain
Post ganglionic neuron	Short	Long
Distribution	Discrete output → gives localized effect	Diffuse output → gives generalized effect
Function	Conservation of energy (anabolic or trophotropic) → **Rest and Digest**	Expenditure/Consume of energy (catabolic or ergotropic) → **"3F" Fight, Flight and Fright**
Neurotransmitter	Acetylcholine	Noradrenaline (except in sweat gland !)
	Essential for life	Not essential for life

Central control of ANS

ANS is controlled by *higher centers in brain*

1- Hypothalamus
2- Medulla oblongata, and others and also spinal cord

Dual innervation by ANS

→ Most organs are innervated by **both** divisions of ANS *"Sympathetic and Parasympathetic"* → They work in harmony together → keeping ***homeostatic balance*** by their opposite actions on the body

Usually ***one system*** *(sympathetic **OR** parasympathetic)* ***predominates*** in controlling the activity of the organ **this is called "Autonomic tone"**

ex. *Heart and GIT* → Parasympathetic predominates
Blood vessels → Sympathetic predominates
Eye → Parasympathetic predominates
Bronchi → Sympathetic predominates

There are certain organs that receive ONLY sympathetic innervation !

1- Blood vessels
2- Sweat glands
3- Pilomotor muscle
4- Kidney
5- Adrenal medulla

Chemical transmission in ANS

Transmission of nerve impulses from
1- one nerve to another or from
2- nerve to effector organ
→ is mediated by chemical mediators
→ called **neurotransmitters**

Main neurotransmitters in ANS

1- **Acetylcholine (Ach)** → released by *"cholinergic nerves"*
2- **Noradrenaline (NA)** → released by *"adrenergic nerves"*
→ And both are called *"autonomic nerves"*

Functions of ANS

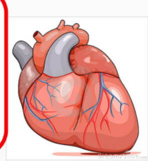
Parasympathetic nervous system

Activated in response to **resting state**

Sympathetic nervous system

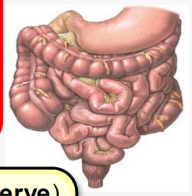
Activated in response to **stressful conditions**

Heart
rate ⇓
force of contraction ⇓
Blood pressure ⇓



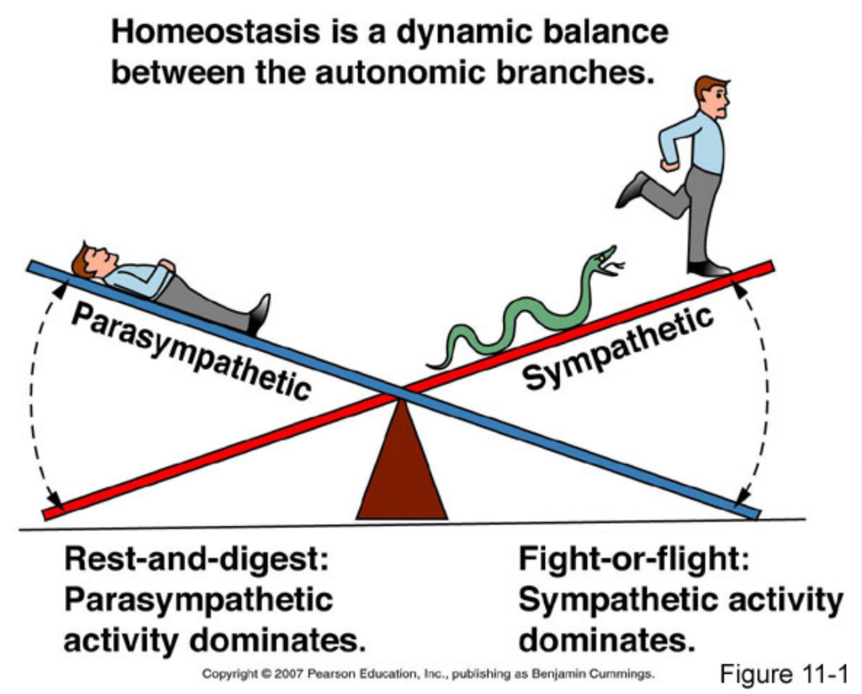
Lungs
Bronchoconstriction

GIT
motility ⇑
blood flow ⇑
sphincter → relaxation



Vagus (Parasympathetic nerve) predominates → keep GIT in contacted state → stimulate *pristalsis* → *"Vagal tone"*

Watery saliva



Homeostasis is a dynamic balance between the autonomic branches.

Rest-and-digest: Parasympathetic activity dominates.

Fight-or-flight: Sympathetic activity dominates.

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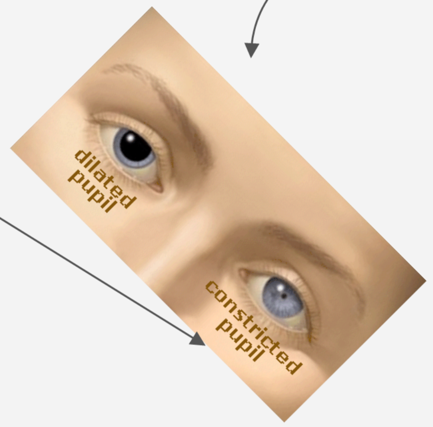
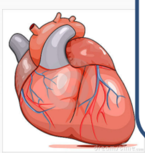
Figure 11-1

Eye
Contraction of *circular muscle* of iris → accommodation for near vision → Constricted pupil → ***Miosis***

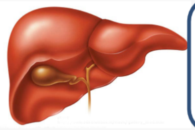
Bladder
Urine evacuation
→ Relaxation of sphincter muscle
→Contraction of detrusor muscle



Heart
rate ⇑
force of contraction ⇑
Blood pressure ⇑ →
Contacted blood vessels



Lungs
Bronchodilatation



Liver
Glycogenolysis
→ ⇑ glucose

GIT
motility ⇓
blood flow ⇓ ,
sphincter will contract

Eye
Dilated eye pupil → ***Mydriasis***

Skeletal muscle blood flow ⇑
(vasodilatation of skeletal muscle blood vessels) ,
Glycogenolysis ⇑

Bladder
Urine retention
→ Relaxation of detrusor muscle
→Contraction of sphincter muscle

Dermal blood flow ⇓

Viscous, little saliva

Fat
Lipolysis → fatty acid libration

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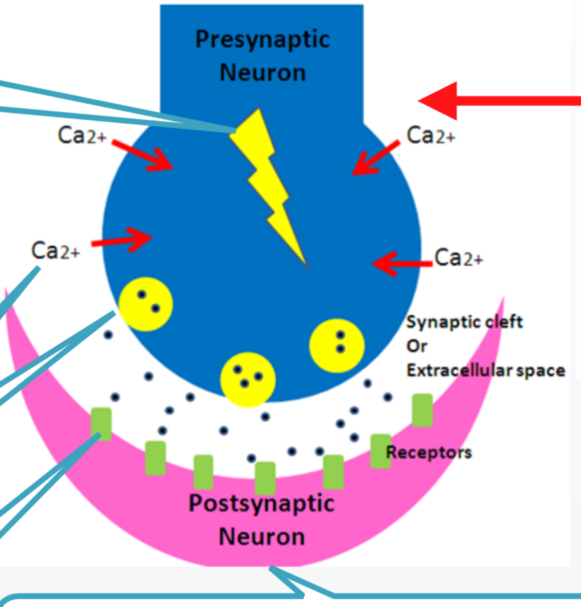
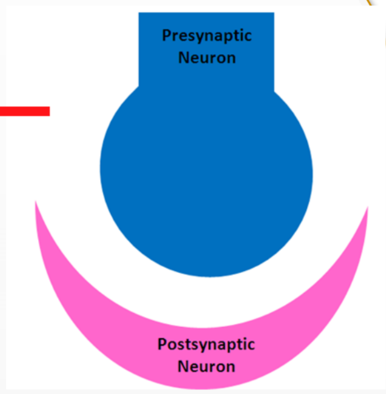
Steps involved in neurotransmission


Presynaptic Neuron
Ca2+
Ca2+
Ca2+
Ca2+
Synaptic cleft Or Extracellular space
Receptors
Postsynaptic Neuron


Presynaptic Neuron
Postsynaptic Neuron

1- The nerve impulses / action potential move through the nerve as waves of depolarization **till reaching the nerve terminal**

We should notice → There is no direct contact between the nerve terminal and the effector organ **so,** connection between the is done by *chemical neurotransmitters in the synapse*

2- Then **influx of Ca^{+2}** ions occurs

3- Vesicles containing neurotransmitter adhere to the synaptic membrane
→ *Release of neurotransmitter by exocytosis*

4- The neurotransmitter bind to its **specific receptor** on the effector organ:
→ **Ach** → binds to cholinergic receptors
→ **NA** → binds to adrenergic receptors

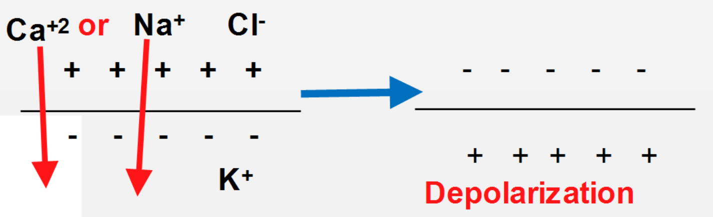
5- This leads to changes in the permeability of cell membrane of the effector organs → leads to initiation of a response in the effector organ ***according to the type of the neurotransmitter***

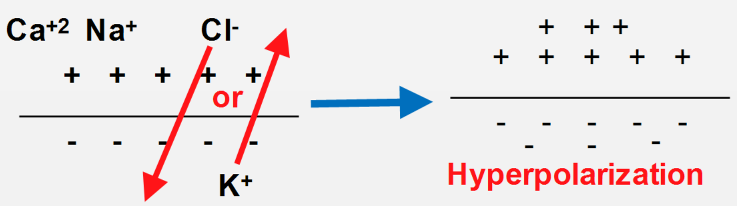
If the neurotransmitter is EXCITATORY to the organ (ex. Ach in smooth muscles)

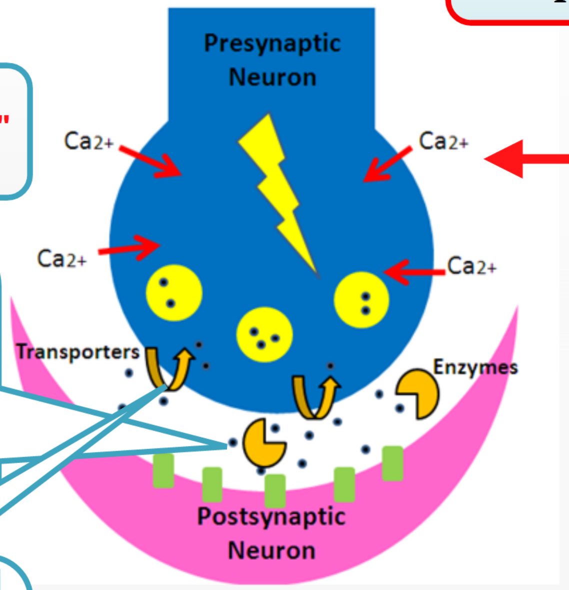
→ Open **Na^{+}** or **Ca^{+2}** channels
→ ⇑ Permeability to Na^{+} or Ca^{+2} ions
→ **influx** (inward diffusion) of Na^{+} or Ca^{+2}
→ **Depolarization** of cell membrane
"Excitatory postsynaptic potential (EPSP)"
→ **Stimulation** of the effector organ
(**ex.** muscle contraction)

If the neurotransmitter is INHIBITORY to the organ (ex. Ach in cardiac muscle)

→ Open **K^{+}** or **Cl^{-}** channels → **influx** (inward diffusion) of **Cl^{-} ions** OR **Outflux** (outward diffusion) of **K^{+} ions**
→ **Hyperpolarization** of cell membrane
"inhibitory postsynaptic potential (IPSP)" → **inhibition** of the effector organ
(**ex.**bradycardia →decreased heart rate)


Ca+2 or Na+ Cl-
+ + + + +
- - - - -
K+
- - - - -
+ + + + +
Depolarization


Ca+2 Na+ Cl-
+ + + + +
or
- - - - -
K+
+ + + + +
- - - - -
Hyperpolarization


Presynaptic Neuron
Ca2+
Ca2+
Ca2+
Ca2+
Transporters
Enzymes
Postsynaptic Neuron

6- Then comes the last step
"Termination of the neurotransmitter response"
which is done by 2 mechanisms

1- Enzymatic destruction

1- Ach is hydrolysed / destroyed by cholinesterases → to choline + acetic acid
2- NA is destroyed by :
a) MAO (monoamine oxidase) → inside nerve terminal
b) and COMT (catechol-o-methyl transferase) → outside nerve terminal

2- Reuptake of transmitter by nerve terminal

to be stored , re-used

1- NA → is reuptaken as a whole
2- Ach → only the choline part is reuptaken to be recombined with the acetate part inside the nerve ending

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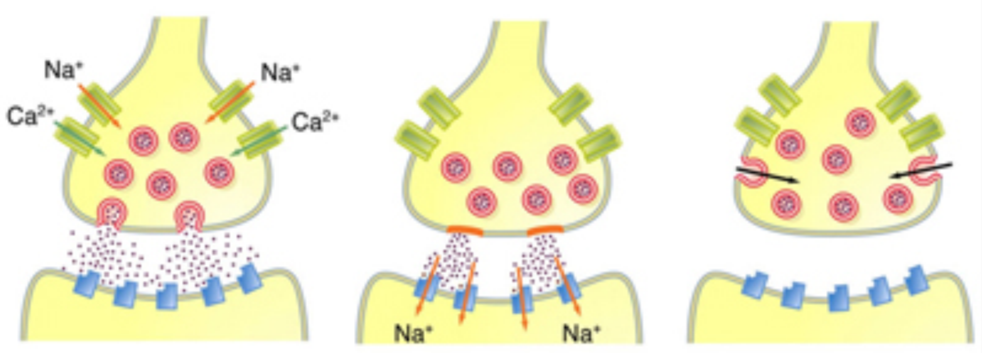
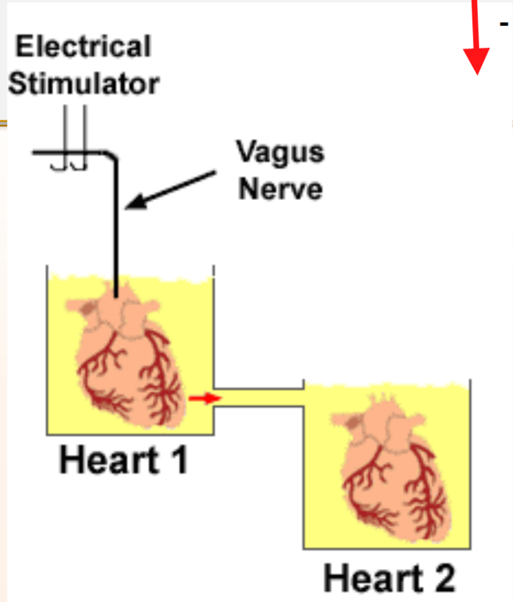

Na+
Na+
Ca2+
Ca2+
Na+
Na+

❶ Transmitter Release ❷ Receptor Activation ❸ Active Termination

Types of cholinesterases

1- True cholinesterase
→ called Acetylcholinesterase
→ **Can not** degrade any substance except acetylcholine
→ Present **only** in CNS and ANS

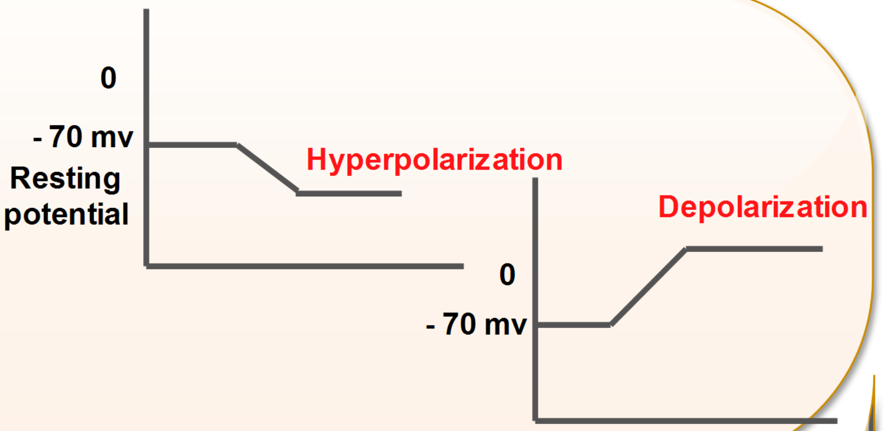
2- Pseudocholinesterase
→ Can degrade acetylcholine and any substance similar to it such as *succinylcholine* (skeletal muscle relaxant)
→ present in other places such as **blood**


Electrical Stimulator
Vagus Nerve
Heart 1
Heart 2

Otto Loewi's experiment

→ 2 isolated hearts of 2 frogs in 2 connected containers contain saline solution

→ Loewi stimulated the vagus nerve of "Heart 1" caused it to **slow down**
→ After a delay he noticed that "Heart 2" also slowed down
→ That **indicated** that some sort of substance "**neurotransmitter** which we now know as **acetylcholine**" flowed from 1 to 2



Autonomic receptors

I Cholinergic rec,

Nicotinic receptors
Central cholinergic rec,

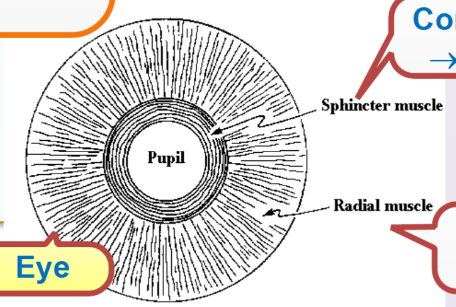
N_N (Nicotinic neuronal)
- **Site**
  - 1- Autonomic ganglia
  - 2- Suprarenal medulla
- **Agonist** — Ach & dil. nicotine
- **Antagonist** — Ganglion blockers **ex.** Hexamethonium & conc. nicotine

N_M (Nicotinic muscular)
- **Site** — Neuromuscular junction (motor end plate) in skeletal muscles
- **Agonist**
  - Ach
  - Anticholinesterases
- **Antagonist** — Curare - Gallamine

Mechanism of action of Nicotinic receptors (CCR)

Channel linked receptor
Ach binds to α-subunit of nicotinic rec, → **open Na^+ channels** → Na^+ influx → Depolarization → EPSP

Nicotinic rec, is composed of 5 subunits "2 α + β + δ + γ"
α subunit → contains Ach binding site



Eye

Contraction → miosis

Contraction → mydriasis

Muscarinc receptors
Peripheral cholinergic rec,

5 types M_1 , M_2 , M_3 , M_4 and M_5
only the first 3 have clinical roles
They are generally **stimulated by→ Ach**
and blocked / **antagonized by→ Atropine**

Mechanism of muscarinic rec, (PCR)
G-protein coupled receptors

M_1
- **Site**
  - 1- Parietal cells of stomach
  - 2- CNS
  - 3- Ganglia
- **Antagonist** — **Selective M_1 blocker** — Pirenzepine & Telenzepine — Decrease HCl ,so used in treatment of peptic ulcer

M_2
- **Site** — Heart
- **M_2 → Gi** → opens *K^+ channels* → *K^+ outflux* → Hyperpolarization → inhibition of cardiac activity

M_3
- **Site**
  - 1- Smooth muscles (GIT , Bronchi , Urinary bladder , eye , uterus)
  - 2- Exocrine glands
  - 3- Vascular smooth muscles

M_4 & M_5 — Recently discovered in the brain (unknown function)

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II Adrenergic rec,

Postsynaptic rec,

α_1
- **Site**
  - 1- Smooth muscles (Cutaneous blood vessels (skin))
  - 2- Radial muscle of iris (eye)
  - 3- GIT
- **Selective agonist** — Methoxamine
- **Selective antagonist** — Prazosin

Mechanism of α_1 rec,
Gq → Activates PLC → ⇑ IP_3 & DAG → ⇑ IP_3 → ⇑ intracellular Ca^{+2} →
- Contraction of vascular smooth muscles (vasoconstriction)
- Contraction of radial muscle of iris (mydriasis)

β_1
- **Site**
  - 1- Heart
  - 2- Juxtaglomerular cells
- **Selective antagonist** — Atenolol

Mechanism of β_1 rec,
Gs → ⇑ cAMP → activates protein kinase → phosphorylation of Ca^{+2} channels in cardiac muscle → **Ca^{+2} influx** → ⇑ *force of contraction* of the heart

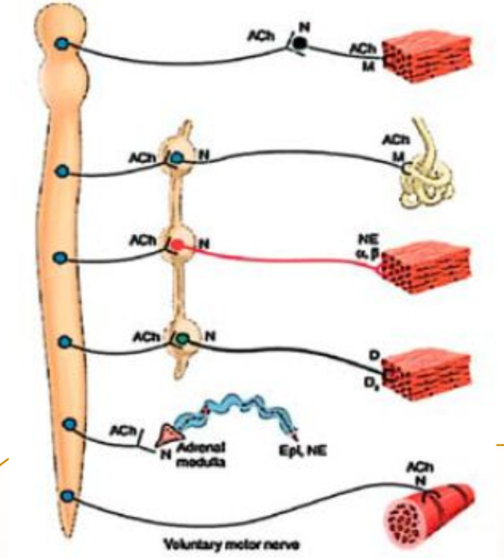
β_2
- **Site**
  - **1- Smooth muscles**
    GIT , urinary bladder , bronchi , uterus
    Blood vessels of skeletal muscles
  - 2- Liver
- **Selective agonist** — Salbutamol — Bronchial smooth muscles relaxation → bronchodilatation used for **Asthma**
- **Selective antagonist** — Butoxamine

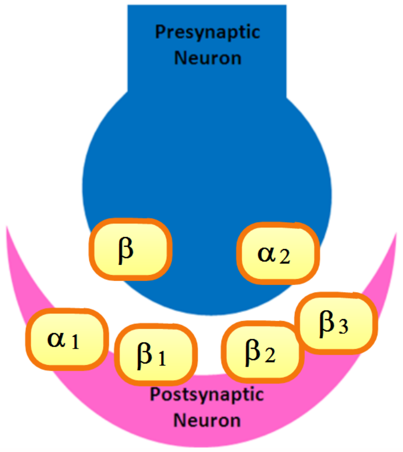
Mechanism of β_2 rec,
Gs → ⇑ cAMP → activates protein kinase → phosphorylation and activation of enzymes responsible for **glycogenolysis**

β_3
- **Site** — Adipose tissue (Fats)

Mechanism of β_3 rec,
Gs → ⇑ cAMP → activates protein kinase → phosphorylation and activation of enzymes responsible for **lipolysis**

- **Non selective agonist** of all α & β rec, is →**Adrenaline**
- **Non selective antagonist** of all α & β rec, is → **Labetalol**
- **Non selective antagonist** at all α rec, are → **Phentolamine & Phenoxybenzamine**
- **Non selective antagonist** at all β rec, is →**Propranolol**

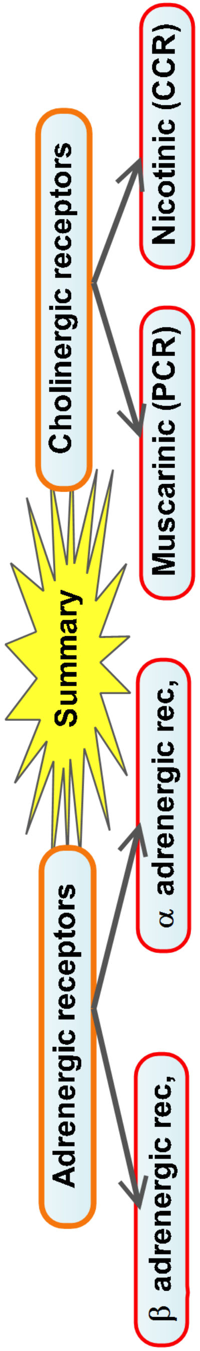




Presynaptic rec,

α_2
- **inhibits** the release of NA
- **Selective agonist** — Clonidine — ⇓ the release of NA → was used in treatment of hypertension
- **Selective antagonist** — Yohimbine — Was used as an aphrodisiac for men → ⇑ sexual desire

β
- **Stimulate** the release of NA
- No clinical use


Summary

Cholinergic receptors

Nicotinic (CCR)

Muscarinic (PCR)

Adrenergic receptors

α adrenergic rec,

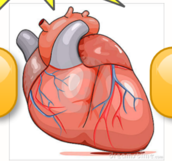
β adrenergic rec,

Receptor name	Site	mechanism	Agonist	Antagonist
N_N	1- Autonomic ganiglia 2- Suprarenal medulla	**Channel linked receptor** Ach binds to α-subunit of nicotinic rec,	Ach dil. nicotine	Ganglion blockers ex. Hexamethonium conc. nicotine
N_M	Neuromuscular junction (motor end plate) in skeletal muscles	→ open Na$^+$ channels → Na$^+$ influx → Depolarization → **EPSP**	Ach Anticholinesterases	Neuromuscular blockers ex. curare Gallamine
M_1	1- Parietal cells of stomach 2- CNS 3- Ganglia	**Gq** → activates *phospholipase C* → ⇑ IP$_3$ & DAG	Ach	Atropine (non selective) Pirenzepine & Telenzepine (selective)
M_2	Heart	**Gi** → opens *K$^+$ channels* → *K$^+$ outflux* → Hyperpolarization → inhibition of cardiac activity	Ach	Atropine (non selective)
M_3	1- Smooth muscles (GIT , Bronchi , Urinary bladder , eye , uterus) 2- Exocrine glands 3- Vascular smooth muscles	**Gq** → Activates PLC → ⇑ IP$_3$ & DAG → ⇑ IP$_3$ → ⇑ intracellular Ca^{+2} → smooth muscles contraction and gland secretion	Ach Muscarine	Atropine (non selective) Oxybutenin (selective)
α1	1- Smooth muscles ex. Cutaneous blood vessels (skin) 2- Radial muscle of iris (eye) 3- GIT	**Gq** → Activates PLC → ⇑ IP$_3$ & DAG → ⇑ IP$_3$ → ⇑ intracellular Ca^{+2} → Contraction of vascular smooth muscles (vasoconstriction) , Contraction of radial muscle of iris (mydriasis)	Adrenaline (non selective) Methoxamine (selective)	Phentolamine & Phenoxybenzamine (non selective) Prazocin (selective)
α2	Presynaptic	**Gi** → inhibits adenyl cyslase → ⇓ cAMP → ⇓ release of NA	Adrenaline (non selective) Clonidine (selective)	Phentolamine & Phenoxybenzamine (non selective) Yohimbine (selective)
β1	1- Heart → 2- juxtaglomerular cells	**Gs** → ⇑ cAMP → activates protein kinase → phosphorylation of Ca^{+2} channels in cardiac muscle → Ca^{+2} influx → ⇑ *force of contraction* of the heart	Adrenaline (non selective) Dobutamin (selective)	Propranolol (non selective) Atenolol (selective)
β2	1- Smooth muscles GIT , urinary bladder , bronchi , uterus Blood vessels of skeletal muscles 2- Liver →	**Gs** → ⇑ cAMP → activates protein kinase → phosphorylation and activation of enzymes responsible for glycogenolysis	Adrenaline (non selective) Salbutamol (selective)	Propranolol (non selective) Butoxamine (selective)
β3	Adipose tissue (Fats)	**Gs** → ⇑ cAMP → activates protein kinase → phosphorylation and activation of enzymes responsible for lipolysis	Adrenaline (non selective)	Propranolol (non selective)

Sympathetic nervous system

Summary

Parasympathetic nervous system

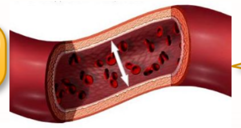


Tachycardia
+ve chronotropic effect — **Heart rate ⇑** — **β1**

+ve inotropic — **Force of contraction ⇑** — **β1**

M2 — **Heart rate ⇓** — Bradycardia
-ve chronotropic effect

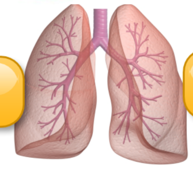
M2 — **Force of contraction ⇓** — -ve inotropic



Blood pressure ⇑ — **Vasoconstriction** — **α1**

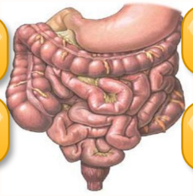
**No parasympathetic innervation
But contain M_3 receptors**

Stimulation of M_3 in endothelial cells of blood vessels → release of NO (Nitric oxide) or EDRF *(Endothelial derieved relaxing factor)* → activates guanyl cyclase → cGMP → **Vasodilatation**



Bronchodilatation — **β2**

M3 — **Bronchoconstriction & ⇑ Secretion**

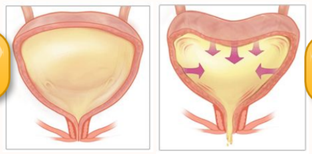


Contraction — **in sphincters' muscles** — **α1**

⇓ Tone & motility — **GIT smooth muscles** — **β2**

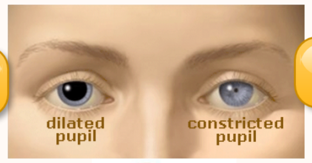
M1 — **in stomach (Parietal cells)** — **⇑ HCl release**

M3 — **GIT smooth muscles** — **⇑ Tone & motility**; **Contraction**



Contraction — **in sphincter muscle** — **α1**; **Urine retention**

M3 — **in detrusor muscle** — **Contraction**; **Urine evacuation**



dilated pupil
constricted pupil

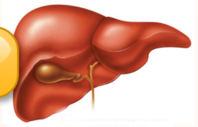
Mydriasis
(Pupil dilatation) — **Radial muscles** — **α1**

M3 — **Circular muscles contraction** — **Miosis**

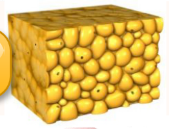
M3 — **Ciliary muscles** — lens accommodation to near vision; **⇓ intraocular pressure**

Relese renin → ⇑ blood pressure
by certain mechanisms — **Juxtaglomerular apparatus** — **β1**

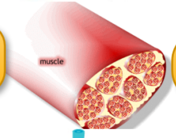
No parasympathetic innervation



⇑ glucose — **Glycogenolysis** — **β2**



⇑ free fatty acids — **Lipolysis** — **β3**



Vasodilatation
of skeletal muscle blood vessels — **β2**

No parasympathetic innervation

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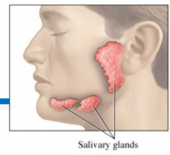
Sweat secretion upon activation of M_3 receptor !

Sweat gland is innervated with sympathetic supply which stimulate it by Ach not NA ! (exception)

M3 — **No parasympathetic innervation**



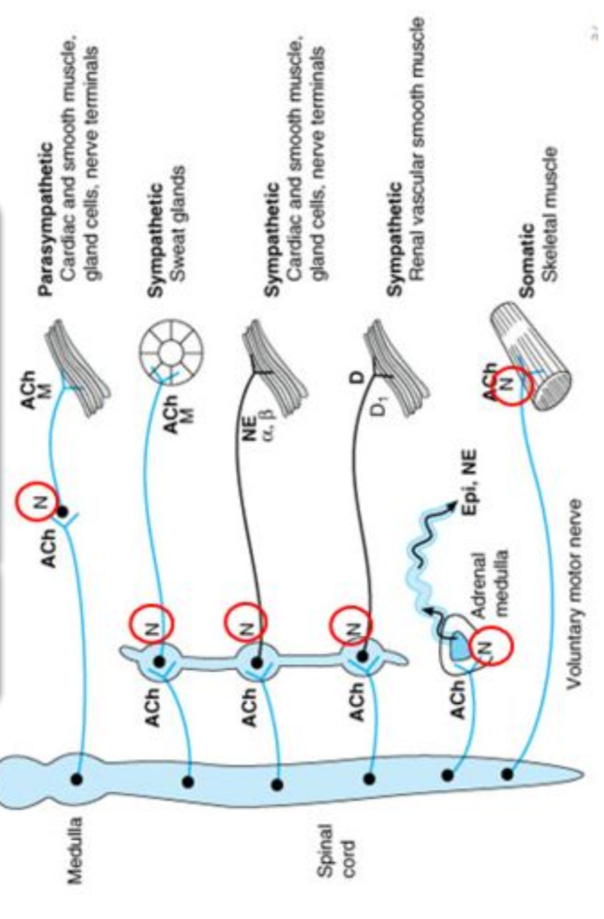
Salivary glands

Viscous secretion (less water)

M3 — **Watery secretion**

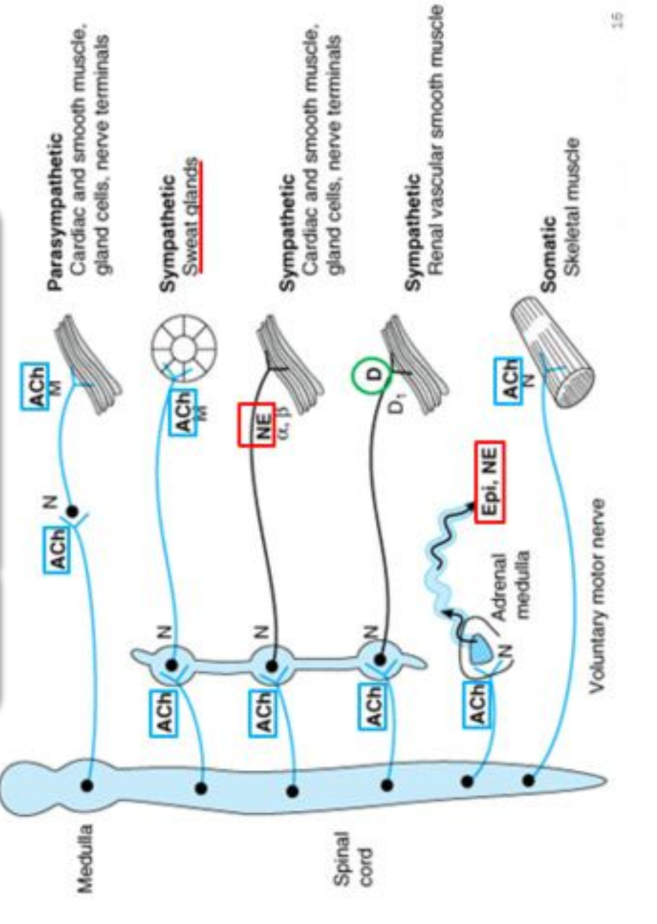
# ⇑ effect of all exocrine glands
ex. salivary - gastric - lacrimal

Receptors summary



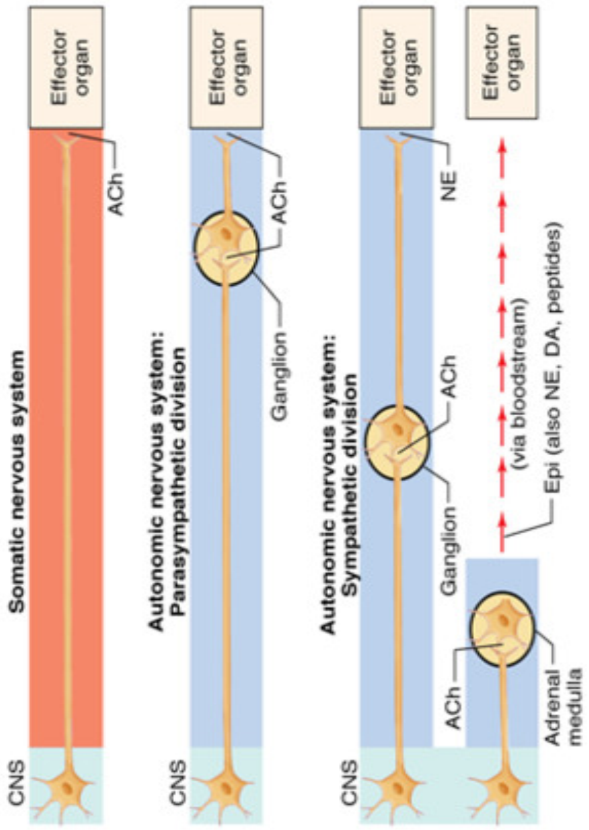
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
Sympathetic
Sweat glands
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
Sympathetic
Renal vascular smooth muscle
Somatic
Skeletal muscle
ACh
M
ACh
N
ACh
M
NE
α, β
D
D1
ACh
N
ACh
N
ACh
N
ACh
N
ACh
N
Epi, NE
Adrenal medulla
Voluntary motor nerve
Medulla
Spinal cord

Neurotransmitter summary



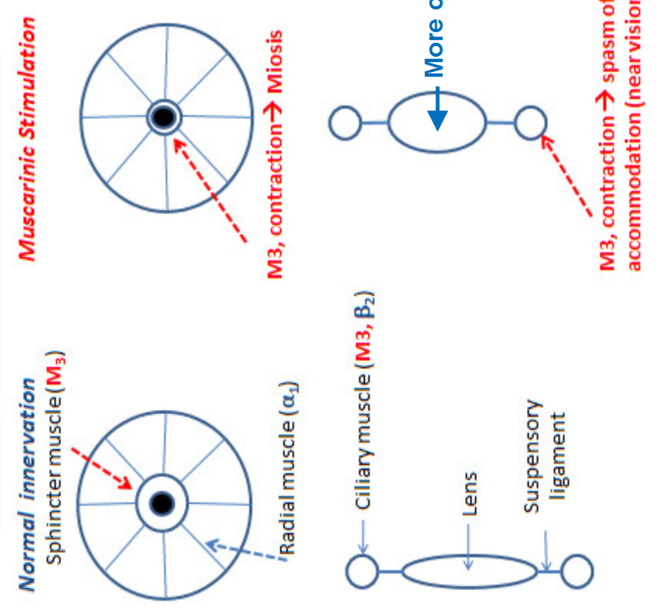
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
Sympathetic
Sweat glands
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
Sympathetic
Renal vascular smooth muscle
Somatic
Skeletal muscle
ACh
M
ACh
N
ACh
M
NE
α, β
D
D1
ACh
N
ACh
ACh
ACh
ACh
Epi, NE
Adrenal medulla
Voluntary motor nerve
Medulla
Spinal cord

Types of nerves



Somatic nervous system
Autonomic nervous system: Parasympathetic division
Autonomic nervous system: Sympathetic division
CNS
CNS
CNS
Effector organ
Effector organ
Effector organ
Effector organ
ACh
ACh
Ganglion
NE
ACh
Ganglion
ACh
Adrenal medulla
Epi (also NE, DA, peptides)
(via bloodstream)

Receptors in the eye



Normal innervation
Sphincter muscle (M_3)
Radial muscle (α_1)
Muscarinic Stimulation
M3, contraction → Miosis
Ciliary muscle (M3, β2)
Lens
Suspensory ligament
More convex lens
M3, contraction → spasm of accommodation (near vision)

Concepts of autonomic disorders

Activity of sympathetic or parasympathetic in certain organ may abnormally increase or decrease causing disorders → that can be treated with drugs working on receptors

Example

If parasympathetic activity to GIT abnormally **increase** → extra ⇑ in motility of GIT → diarrhea and colics
So, using of a drug that ⇓ GIT motility (like atropine) may help in this case

and If parasympathetic activity to GIT abnormally **decrease** → extra ⇓ in motility of → Atony / paralytic ileus
So, using of a drug that ⇑ GIT motility (like Ach) may help in this case

Autonomic drugs

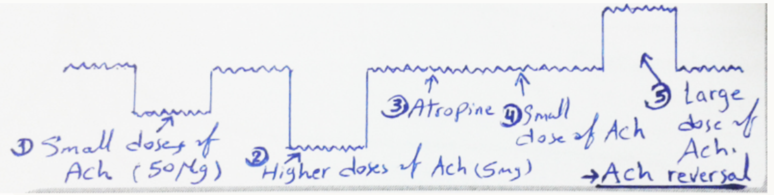
Parasympathomimetics	Stimulate muscarinic rec,
Parasympatholytics	Block muscarinic rec,
Sympathomimetics	Stimulate α & β rec,
Sympatholytics	Block α & β rec,
Ganglionic stimulants	Stimulate N_N rec,
Ganglionic blockers	Block N_N rec,

Pharmacological action of Acetylcholine

1. Muscarinic actions	2. Nicotinic actions
- Smooth muscles - Cardiac muscle - Exocrine glands ✓	- Autonomic ganglia - Adrenal medulla - Skeletal muscles (MEP)

A. Effect on autonomic ganglia & adrenal medulla (N_N)

Ach reversal experiment using anesthetized cat blood pressure



- Small dose of Ach → ⇑ blood pressure due to → *"vasodilatation and bradycardia"*
- Higher dose of Ach → **Further** ⇑ in blood pressure
- Atropine → **block** muscarinic receptors, **so:**
- ***Small dose*** of Ach after atropine → gives no effect
- **At high dose** of Ach after atropine → ⇑ blood pressure **due to:**

1. Stimulation of N_N receptor in *adrenal medulla* release of NA and AD → *"Vasoconstriction and tachycardia"* → ⇑ blood pressure
2. Stimulation of N_N receptor in *sympathetic ganglia*

# Muscarinic actions of Ach are stronger ,so they mask nicotinic actions
# Stimulation of nicotinic receptor needs high doses of Ach

1- Parasympathomimetics

- Called also → Cholinergic drugs / Cholinomimetic drugs
- Are drugs which stimulate muscarinic receptors (PCR)

Directly acting

- **1) Choline esters**
  - Acetylcholine
  - Carbachol
  - Methacholine
  - Bethanecol
- **2) Cholinomimetic alkaloids**
  - Pilocarpine
  - Muscarine
  - Arecoline

Indirectly acting

- **3) Anticholinesterases** — *Indirectly stimulate muscarinic receptors*
  - **Reversible**
    - Physostigmine
    - Neostigmine
    - Neostigmine substitute
  - **Irreversible**
    - Organophosphorous compounds
      - **DEP :** Di-isopropyl fluorophosphate
      - **TEPP :** Tetraethyl pyrophosphate
      - **Nerve gases :** Tabun - Suman - Sarin
      - **Insecticides :** Parathion - Malathion - Fenthion

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B- Effect of Ach on Skeletal muscles

Stimulation of **N_M** receptor in motor end plate of skeletal muscles → causes **muscle twitches**

Use of Ach
Not used now due to

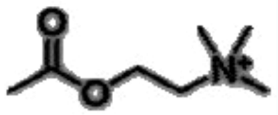
1- Not effective orally (Must be parenteral)
2- Short duration of action
3- Non selective (Muscarinic & Nicotinic actions)

# So, used as experimental tool

1- Parasympathomimetics

1) Choline esters

I. Acetylcholine



Acetylcholine (Ach) is a neurotransmitter at

1- *Neuromuscular* junction (N_M)
2- Autonomic *ganglia* (N_N)
3- *Preganglionic* nerve to adrenal medulla (N_N)
4- **Postganglionic parasympathetic** nerve endings **(M)**
5- Postganglionic **sympathetic** nerve endings of **sweat glands (M)**
6- Some areas in CNS (**M**)

Synthesis of Ach in nerve terminal

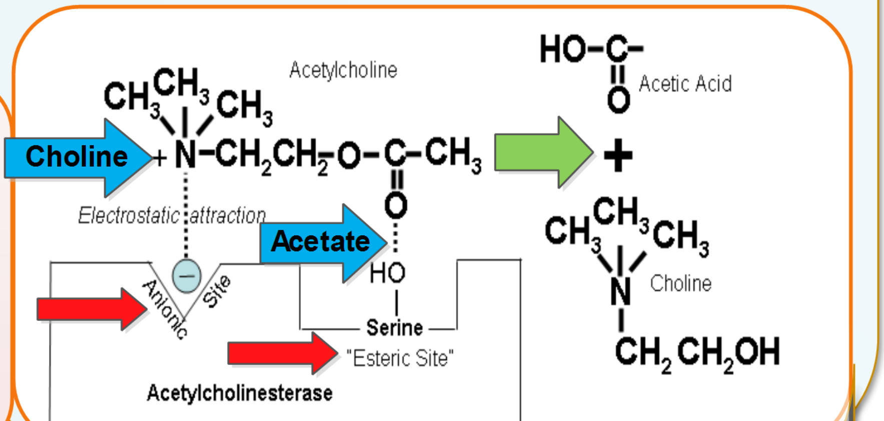
$$\text{Acetate + CoA} \xrightarrow{\text{ATP} \rightarrow \text{ADP}} \text{Acetyl CoA}$$

$$\text{Acetyl CoA + Choline} \xrightarrow[\text{or Choline acetylase}]{\text{Choline acetyl transferase}} \text{Acetylcholine}$$

Hydrolysis of Ach by cholinesterases

True cholinesterase (acetylcholinesterase)	Pseudocholinesterase (Butyrocholinesterase)
Specific: Hydrolysis of Ach and methacholine	*Non-specific*: Hydrolysis of Ach ,Succinylcholine and procaine
Site: Cholinergic sites and CNS	*Site*: Blood and liver

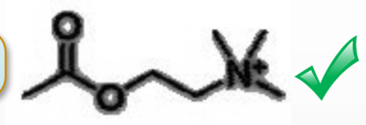
Acetylcholine has a **short duration of action** as it is rapidly hydrolysed by cholinesterase into **Acetate + Choline**



1- Parasympatho*mimetics*

1) Choline esters

I. Acetylcholine



II. Synthetic choline esters

Properties
- Resist hydrolysis by cholinesterase → more stable
- Longer duration of action
- Active orally and parenterally
- More selective

Types of modification
- **β-methylation of Ach** → ⇑ selectivity to muscarinic activity **ex.** Methacoline
- **Carbamate ester**→ resist hydrolysis by cholinesterase → longer duration of action **ex.** Carbachol

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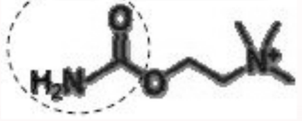
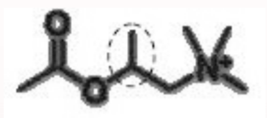
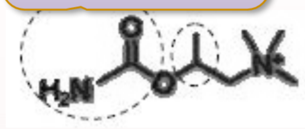
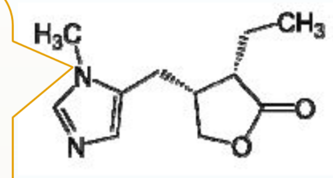
	1- Carbachol	**2- Methacholine**	**3- Bethanecol**
Structure			
Modifications	Carbamate instead of ester	β-methylation	Both modifications
Properties	1. Resist hydrolysis by cholinesterase enzyme → so it has longer duration of action 2. Non selective → has *muscarinic and nicotinic* actions 3. Due to non selectivity → it is used locally in the eye → miosis and ⇓ IOP	Selective muscarinic actions "NO nicotinic actions", it is more *selective to CVS* → decrease heart rate & Vasodilatation	1. Selective muscarinic actions "NO nicotinic actions", it is more *selective to smooth muscles* (GIT - Urinary bladder - Eye) 2. Resist hydrolysis by cholinesterase enzyme → so it has longer duration of action 3. Active orally
Uses	Used in **glucoma** (increased intraocular pressure)	1. Paroxysmal atrial tachycardia 2. Raynaud's disease (peripheral vasoconstriction)	1. Retention of urine →postoperative & postpartum 2. GIT disorders →paralytic ileus → gastric atony 3. Ophthalmic → Glucoma

2) Cholinomimetic alkaloids

Pilocarpine



Properties

1. Tertiary amine → lipid soluble → that means it can ***cross BBB*** → causes CNS stimulation *(so, used locally in the eye)*
2. It has mainly **muscarinic effects**
3. NOT hydrolyzed by cholinesterase enzyme → long duration of action

Mechanism of action

Direct **stimulation of muscarinic receptors**

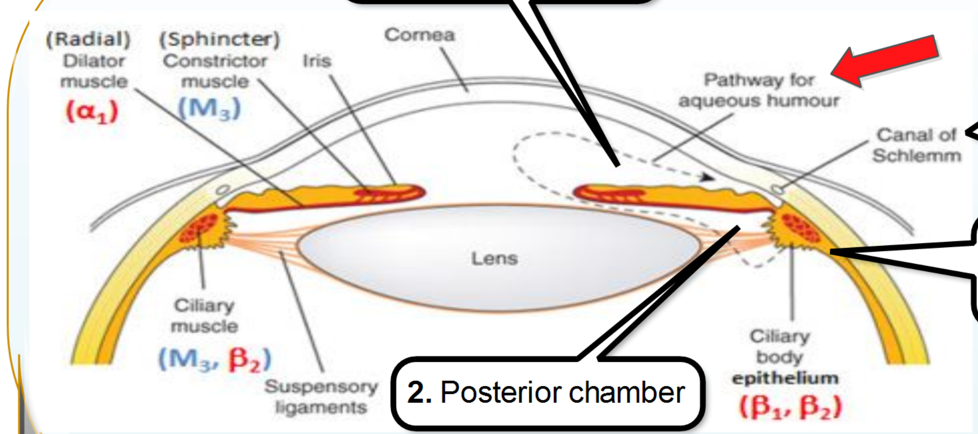
Pharmacological actions

1. CNS → Cortical stimulation → irritability - nervousness - insomnia → so, used locally on the eye
2. GIT → ⇑ tone and motility (Peristalsis)
3. Urinary bladder → evacuation
4. Bronchi → bronchoconstriction
5.⇑ Secretion of exocrine glands →
a) ⇑ Saliva (sialagogue)
b) ⇑ Sweat (diaphoretic)
6. Eye →
a) Contraction of circular muscles of iris (constrictor pupillae muscles) → miosis → widening of angle of filtration (angle of anterior chamber) → drainage of aqueous humour → ⇓ **IOP**
b) Contraction of cilliary muscles
1- accomodation for near vision
2- opening of canal of schlemm → ⇑ drainage of aqueous humour → ⇓ **IOP**

Therapeutic uses

1. Glaucoma
2. Overcome mydriatic action produced by atropine
3. Antidote to atropine overdose
4. Alternative with mydriatics → to break adhesion between iris and lens
5. Stimulate salivation in patients with dry mouth
6. Promote hair growth (not autonomic function) !

Glaucoma



(Radial) Dilator muscle (α_1)
(Sphincter) Constrictor muscle (M_3)
Iris
Cornea
Pathway for aqueous humour
Canal of Schlemm
Lens
Ciliary muscle (M_3, β_2)
Suspensory ligaments
Ciliary body epithelium (β_1, β_2)

3. Anterior chamber

2. Posterior chamber

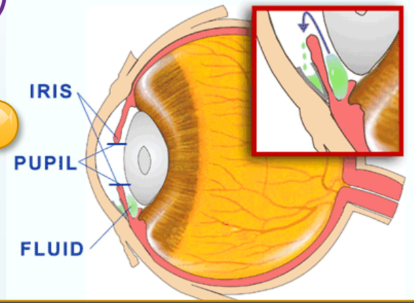
4. Drainage at angle of filtration and **canal of schlemm**

1. Aqueous humour
Secreted from **ciliary body**

Types of humors in the eye

1- Aqueous humor *(between cornea and lens)*
2- Vitrous humor *(in the eye mass)*

Normal



Intraocular pressure

Secretion > Drainage

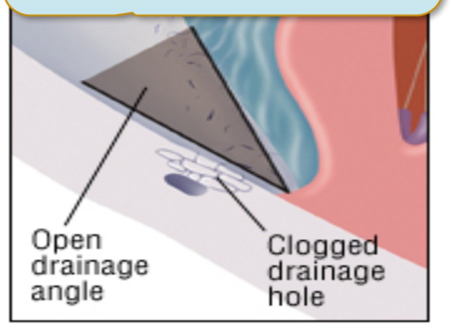
It increases when the rate of aqueous humor secretion becomes **more than** its drainage (equilibrium imbalance) → leading to **glucoma (IOP ⇑)** → this can cause extra pressure on optic nerve → may lead to irriversible blindness

Glaucoma types

1. Open angle glaucoma

⇑ **intraocular pressure** due to gradual degeneration of canal of schlemm

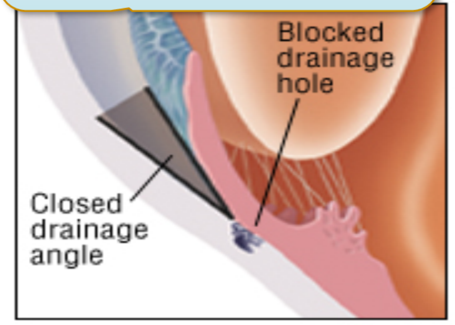
- Chronic
- Gradual
- Bilateral

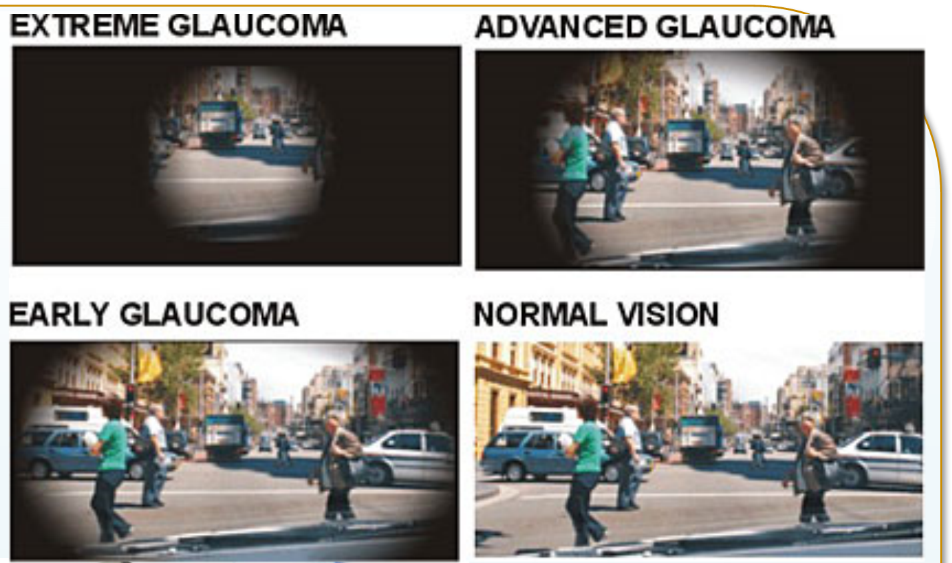


2. Closed angle glaucoma

⇑ **IOP** due to sudden abnormal narrowing / closure of angle of filtration *(angle between iris & cornea)*

- Acute
- Painful
- Unilateral





Treatment

1. Miotics (Pilocarpine)
2. β_2 blockers (Timolol)
3. Carbonic anhydrase inhibitors
   - Brinzolamide (Azopt® - Alphagan®)
   - Dorzolamide (Cosopt® - Xola® - Trusopt®)
4. Prostaglandin analogues
   - Latanoprost (Xalatan®)
5. Surgery

تيمولول
TIMOLOL
AZOPT
Alcon
Alphagan
ALLERGAN

Cosopt
2%
0.5%
5 ml
Xola
زولا
Xalatan
0.005 %

Ph. Alaa Nasr

Indirectly acting cholinergic drugs

3) Anticholinesterases

Mechanism of action

They **inhibit cholinesterase enzyme** → preventing hydrolysis of Ach → **accumulation of Ach** at cholinergic receptors → so, its **effect** ⇑ *(exaggerated parasympathetic activity)* "but they do not interact with receptors"
→ That leads to muscarinic and nicotinic effects **(Non selective)**

I. Reversible anticholinesterase

	1- Physostigmine	2- Neostigmine
Properties	Tertiary amine → **lipid soluble** → cross **BBB** → CNS stimulation → restlessness - tremors - headache - insomnia → So, used locally in the eye	Quaternary ammonium salt → **NON lipid soluble** → **1.** Can not cross **BBB** → Advantage *(no CNS stimulation)* **2. Poorly** absorbed orally → disadvantage *(given by injection)*
Mechanism	As said before	As said before
Pharmacological actions	**1. Stimulation of M_3 receptor in the eye** **a)** Circular muscle → miosis → ⇓ IOP **b)** Ciliary muscle → accomodation for near vision **2. Nicotinic effect** → twiches in eye lid muscles due to activation of N_M receptor	**1. Stimulation of muscarinic receptors** GIT , eye , UT , heart and bronchi **2. Nicotinic effect** → twitches in skeletal muscles due to activation of N_M receptor
Therapeutic uses	**1.** Glaucoma **2.** Overcome / counteract effect of mydriatics (atropine like drugs) **3.** Alternative with mydriatics → to break adhesion between iris and lens **4.** Antidote to atropine overdose / toxicity (centerally and peripherally) **5.** Early stage of Alzheimer's dementia **(**degeneration of cholinergic neurons → loss of memory**)** # Physostigmine → ⇑ Ach level in brain	**1.** Glaucoma **2.** Paralytic ileus (decreased GIT motility) **3.** Postoperative urine retention **4.** Antidote to competitive NMB **ex.**curare **5. Myasthenia gravis**

3- Neostigmine substitutes

Edrophonium
- Very short duration of action (5 min) → so, used for **diagnosis** of **myasthenia gravis** *(brief improvement)*
- used for **treatment** of **myasthenia gravis**

Pyridostigmine
Ambenonium

Advantages
1. More selective on skeletal muscles
2. Effective orally
3. Longer duration of action

Demecarium
- **Treatment** of **glaucoma** *(long acting miotic)*

Tacrine & Donepizil
- **Treatment** of **Alzhiemer's disease**

APEX Pharma
DONHIMER
5mg
Donepezil HCl
10 F.C. Tablets

Myasthenia gravis

Disease of **abnormal fatigue of skeletal muscles** characterized by
1. decreased grip strength
2. Ptosis (dropped eyelid)
3. difficulty in chewing , swallowing , lifting objects , holding the head up and speaking

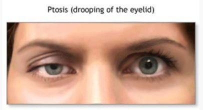
depending on the severity

Aetiology

Abnormalities in N_M receptors at motor end plate due to an **autoimmune disease** (production of antibodies against N_M receptors)

Treatment

Neostigmine + Atropine


Ptosis (drooping of the eyelid)

- **Neostigmine**
  → direct stimulation of skeletal muscles
  → Anticholinesterase → ⇑ **Ach** → stimulation of skeletal muscles
- **Atropine**→ block undesired muscarinic effects of Ach

3) Anticholinesterases

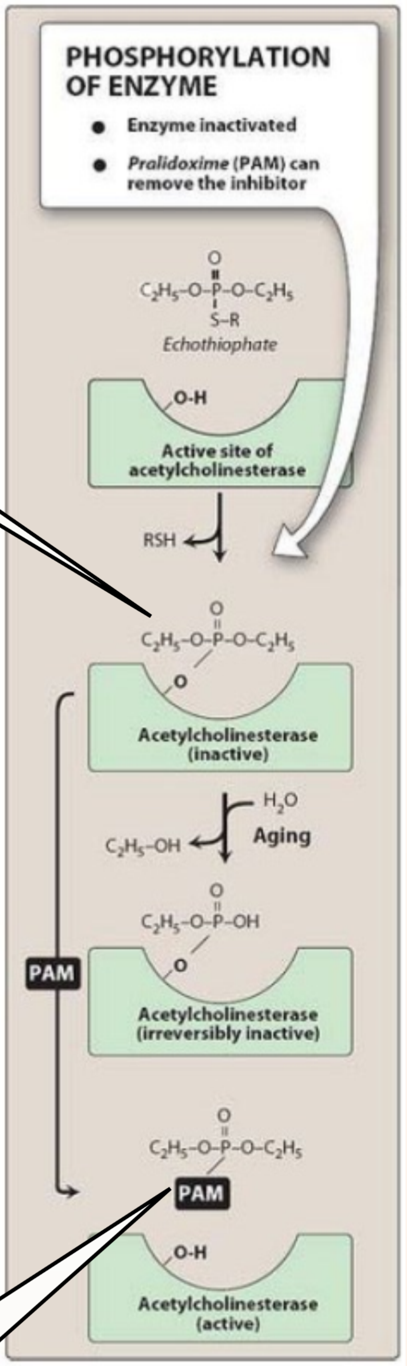
II. Irreversible anticholinesterase

Organophosphates

Ph. Alaa Nasr

Mechanism

- They form **strong covalent bond with cholinesterase** enzyme → leading to **permanent inactivation** of the enzyme
- Enzymatic activity is returned by **synthesis of new enzyme !**


PHOSPHORYLATION OF ENZYME
Enzyme inactivated
Pralidoxime (PAM) can remove the inhibitor
C2H5-O-P-O-C2H5
S-R
Echothiophate
O-H
Active site of acetylcholinesterase
RSH
O
Acetylcholinesterase (inactive)
H2O
Aging
C2H5-OH
C2H5-O-P-OH
Acetylcholinesterase (irreversibly inactive)
PAM
Acetylcholinesterase (active)

Therapeutic uses

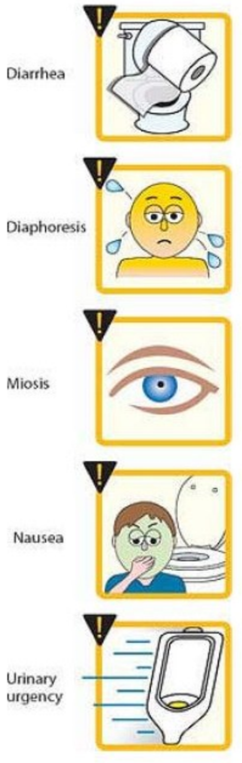
1. **DFP (diisopropyl fluorophosphate)** → used in treatment of ***glaucoma***
2. **Insecticides** → Parathion - Malathion - Fenthion
3. **Nerve gases** → Tabun - Soman - Sarin ***(war gases)***

Toxicity

1. **SLUD syndrome** → Salivation + Lacrimation + Urination + Diarrhea
2. Severe bronchospasm
3. Bradycardia
4. Miosis
5. Skeletal muscle twitches
6. **CNS stimulation** → tremors - convulsions - confusion
→ depression of cardiovascular and respiratory centers

Treatment of toxicity

1. Atropine
2. Cholinesterase re-activator as
Pralidoxime (PAM) - Diacetylmonoxime (DAM)
→ Combine with phosphate of organophosphorous compounds → *leave cholinesterase free*
→ Must be given **within 3-4 hours (before aging of the enzyme** → organophosphate binds to cholinesterase enzyme and loses one of its alkyl group)


Diarrhea
Diaphoresis
Miosis
Nausea
Urinary urgency

Side effects of cholinergic drugs

1. Sweating (diaphoresis)
2. Salivation
3. Hypotention
4. Nausea , diarrhea and abdominal pain
5. Urinary urgency
6. Bronchospasm

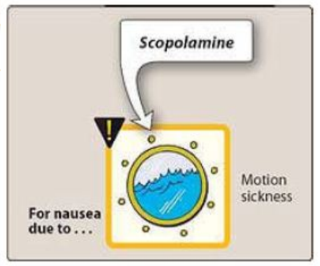
Contraindications of parasympathomimetics

1. **Peptic ulcer** → as they increase gastric acid secretion
2. **Bronchial asthma** → as they may induce bronchospasm
3. **Coronary insufficiency** → as they may cause hypotention → leading to further decrease in coronary blood flow

2- Parasympatholytics

Parasymathetic antagonist
Anticholinergic drugs
Antimuscarinic drugs

Are drugs which block *muscarinic action of Ach and related drugs* by blocking muscarinic receptors (PCR)


Scopolamine
For nausea due to . . .
Motion sickness

II. Hyoscine (Scopolamine)

Similar to atropine in action

Shorter duration of action

Differs from atropine in

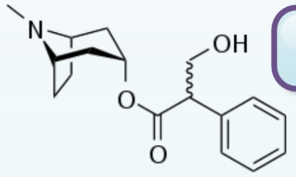
Effect is more pronounced on the eye and exocrine glands

Sedation and hypnosis

Mainly CNS depressant

- Amnesia (temporarily loss of memory)
- Anti motion sickness

- So used as preanesthetic medication
- Decrease the dose of general anesthetic

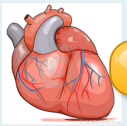


I. Atropine (Hyoscamine)

Mechanism

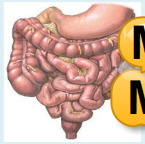
Reversible competitive antagonist of Ach at muscarinic receptors
Antagonism effect is overcome by increasing Ach level ex. using anticholinesterases

Pharmacological actions

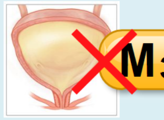


Heart rate ⇑ — Tachycardia +ve chronotropic effect

No effect on blood pressure — **No parasympathetic innervation**



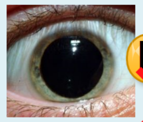
- ⇓ **HCl release**
- ⇓ **Tone & motility** — **Constipation**
- **Relaxation of detrusor muscle**



Urine retention
- **Contraction of sphincter muscle**
- **Relaxation of ureter muscle (antispasmodic)**

Bronchodilatation & ⇓ Secretion

- **Therapeutic doses**
  - **Antiemetic** (inhibit vomiting center)
  - **Antiparkinsonian** (decrease tumors)
- **Toxic doses** — **CNS stimulation**



- **Mydriasis** — Due to block of M_3 receptor in **circular muscle** → **Passive mydriasis**
  - **So contraindicated in glaucoma patients**
- **Increase IOP**
- **Cycloplegia** — Due to block of M_3 receptor in **ciliary muscle (causing paralysis in it)** → **loss of accomodation for near vision**
- **Loss of light reflex** — Normal reflex to light is lost due to the **paralysis of circular muscles** (responsible for miosis)

Exocrine glands

- ⇓ **secretions** → salivary (Xerostomia → dry mouth), ⇓ bronchial secretion and lacrimation
- ⇓ **Sweat body** → ⇑ **temperature** → **atropine fever**

2- Parasympatholytics

III. Synthetic atropine substitutes

Mydriatics

1. Homatropine
2. Eucatropine
3. Tropicamide (Mydrapid®)
4. Cyclopentolate (Plegica®)

They do not have to be selective as they are administered locally in the eye

Mydrapid
0.5%

Antisecretory / Antispasmodic

1. Hyoscin butyl bromide (Buscopan®)
2. Propantheline
3. Oxyphenonium
4. Atropine methylnitrate

They are used for colics (intestinal - renal - bilary)

Buscopan
Boehringer Ingelheim

Antiparkinsonian

1. Benztropine (Cogintol®)
2. Benzhexol

Must be lipophilic to cross BBB

For bronchial asthma / bronchdilator

1. ibratropium (Atrovent® - Combivent®)
2. Oxitropium

Atrovent
20 mcg/puff
Boehringer Ingelheim

Combivent
Unit Dose Vials

Urinary bladder relaxants

1. Oxybutenin (Uripan®)
2. Tolterodine (Uricontrol®)

They are selective **M₃** receptors blockers (in detrusor muscle of urinary bladder Used in treatment of urine incontinence and nocturnal enuresis

UriControl
Tolterodine tartrate

TOLTERODINE

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Therapeutic uses of antimuscarinic drugs

GIT

1. Antispasmodic:
Colics (intestinal - bilary) - diarrhea - irritable colon
2. Antisecretory: in peptic ulcer

# Pirenzepine (selective M₁ blocker) is preferred over atropine in peptic ulcer

CNS

a) Preanesthetic medication:
Hyoscine is more preferred due to:
1. amnesia
2. antisecretory
3. protect heart from vagal effect

b) Antiparkinsonian:
⇓ tremors and rigidity

Ophthalmology

1. Fundus examination:
Mydriasis → to examine retina and optic disc
2. Alternative with miotics: to break adhesion between iris and lens

Urinary tract

1. Urinary incontinence
2. Nocturnal enuresis
3. Antispasmodic for renal colics

Prophylaxis against motion sickness

Hyoscine is the drug of choice

Respiratory

Bronchodilators in bronchial asthma
Disadvantage → atropine produce viscid thick sputum → difficult to expel

Antidote for poisoning by

Mushrooms - Neostigmine - Physostigmine - Organophosphates

CVS

Carotid sinus bradycardia
hyperactive carotid sinus → reflex bradycardia

Skin

For treatment of hyperhydrosis (excessive sweating)

Adverse effects and toxicity of atropine

1. Tachycardia (rapid pulse)
2. Mydriasis (Dilated pupils) → photophobia
3. Dry mouth
4. Flushed skin
5. High body temperature (atropine fever) specially in children
6. CNS (restlessness - confusion)
7. Urine retention

Antidote: Physostigmine (can cross BBB) or Pilocarpine

Contraindications of antimuscarinics

1. Glaucoma
2. Enlarged prostate (prostatic hypertrophy) may cause urine retention
3. Angina pectoris as atropine causes tachycardia
4. Paralytic ileus
5. Esophageal reflux

3- Sympathomimetic

Are drugs which stimulate adrenergic receptors (PCR) → produce effects similar to sympathetic nerve stimulation

Classification

A- Chemically

- **1. Catecholamines**
  - 1) Adrenaline
  - 2) Noradrenaline
  - 3) Dopamine
  - 4) isoprenaline
- **2. Non catecholamines**
  - 1) Ephedrine
  - 2) Amphetamine
  - 3) Phenylephrine
  - 4) Tyramine

B- According to mechanism of action

- **1. Direct**
  - Drugs stimulate α or β receptors *directly*
  - **ex. 1.** Adrenaline , **2.** Noradrenaline **3.** isoprenaline , **4.** Phenylephrine
- **2. Indirect**
  - Drugs act by *release NA from nerve terminal* **then** NA stimulate adrenergic receptors
  - **ex. 1.** Amphetamine , **2.** Tyramine
- **3. Dual / Mixed action**
  - Drugs act by *both direct and indirect mechanisms*
  - **ex. Ephedrine**

I. Catecholamines

- They are called catecholamines as they contain catechol (3,4-dihydroxyphenyl group) in their structures.
- They are derived from the amino acid "Tyrosin"

1- Adrenaline (Epinephrine)

- Directly acting
- Stimulate all adrenergic receptor α **and** β receptors
- Secreted from the **adrenal medulla**

Adrenal medulla secretes 80% Adrenaline and 20% Noradrenaline

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1) Synthesis

Tyrosine — *Enters the nerve terminal*

⇓ Tyrosine hydroxylase

DOPA (dihydroxyphenylalanine)

⇓ DOPA decarboxylase

Dopamine — *Enters the vesicles*

⇓ Hydroxylation (dopamine hydroxylase)

Noradrenaline

⇓ Methylation → in Adrenal medulla

Adrenaline

These steps occur in different locations in the body but it stops at a suitable product to produce a suitable function !

In adrenal medulla → the synthesis goes to the end (formation of **Adrenaline / Epinephrine**)

In symaphetic nerve endings → it stops at the formation of **Noradrenaline**

In dopaminergic neurons → it stops at the formation of **dopamine**

2) Termination of action

a. Enzymatic destruction

Adrenaline , Noradrenaline & all catecholamines

⇓ MAO - COMT

- MAO: Monoamine oxidase → inside the nerve terminal
- COMT: Catechol-O-methyl transferase → in the synapse

3-methoxy, 4-hydroxy mandelic acid **Vanillyl mandelic acid (VMA)**

VMA can be used as a pheochromocytoma marker !!

Pheochromocytoma → is a tumor of adrenal medulla → causes secretion of LARGE amount of adrenaline → that leads to hypertension

So HOW can it be used as a marker !

VMA is excreted in urine in a normal level → 2-6 mg/ 24 hrs in case of pheochromocytoma → the level increases can exceed 50 mg/ 24 hrs !

b. Uptake mechanisms

Most of released NA undergoes neuronal uptake after performing their actions

- **1. Neuronal uptake (Uptake 1)**
  - **Blockers** → Cocaine , Guanethidine
  - increase NA level at receptors' site
- **2. Extraneuronal uptake (Uptake 2)**
  - Catecholamines go to tissues
  - **Blockers** → Phenoxybenzamine
- **3. Granular uptake (Uptake 3)**
  - Catecholamine is taken up from the cytoplasm (inside the nerve terminal) → to be stored in vesicles
  - **Blockers** → Reserpine

3) Absorption of adrenaline

- **Oral**
  - **Poor absorption** → rapid destruction by intestinal enzymes
- **Parenteral**
  - **Subcutaneous SC**
    - **Slow absorption** → due to local vasoconstriction (α_1 stimulation → ⇓ blood flow → ⇓ absorption)
  - **Intramuscular IM**
    - **Rapid absorption** → due to vasodilatation of skeletal muscles blood vessels (β_2 stimulation → ⇑ blood flow → ⇑ absorption)
- **inhalation**
  - Used for its **local effect** on respiratory tract

1- Adrenaline (Epinephrine)

- Synthesis ✓
- Termination of action ✓
- Absorption of adrenaline ✓
- Pharmacological actions

A. Local actions

1. Mucous membranes

Vasoconstriction (α_1 stimulation) so used as

1. Hemostatic → produces vasoconstriction which ⇓ bleeding → so can be applied to bleeding surfaces

2. Decongestant → applied locally in the nose → ⇓ congestion by vasoconstriction in nasal blood vessels

3. Used with local anesthetics → produces vasoconstriction → ⇓ absorption → prolongs the effect of anesthetics

2. Eye

limited effect as adrenaline is destroyed by alkaline tears

Adrenaline ⇓ formation of aqueous humor and ⇓ IOP

B. Systemic actions

*Adrenaline directly stimulate both α **and** β receptors*

The effect produced depends on

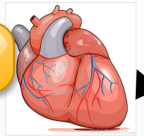
1. Concentration of adrenaline

2. Type of receptor

◆ At **high** concentration → α effect predominates

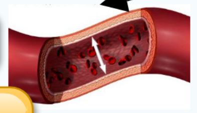
◆ At **low** concentration → β effect predominates

CVS



β_1:

- **Heart rate ⇑** — Tachycardia +ve chronotropic effect
- **Force of contraction ⇑** — +ve inotropic
- **Cardiac output ⇑**
- **Cardiac work and O_2 consumption ⇑** — So dangerous in angina



- α_1: **Vasoconstriction** of skin and mucous membrane blood vessels
- β_2: **Vasodilatation** of skeletal muscles blood vessels

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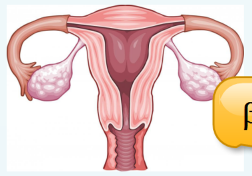
Blood pressure

- **Large doses of Adrenaline** → ⇑ blood pressure due to vasoconstriction → α effect predominates
- **Low doses of Adrenaline** → ⇓ blood pressure due to vasodilatation → β effect predominates
- **Adrenaline reversal !!**



β_2:

- **Relaxation of pregnant uterus**
- Effects depend on menstrual and gestation state

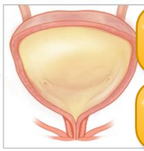
β_2:

- **Vasodilatation** of skeletal muscles blood vessels → **⇑ blood flow**
- Facilitates neuromuscular transmission
- Hastens recovery from fatigue

Secretions of exocrine glands **decrease** → due to vasoconstriction of blood vessels supplying them

Smooth muscles

- α_1: Contraction in sphincters' muscles
- β_2: **⇓ Tone & motility**



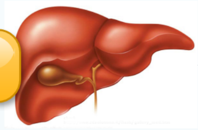
- α_1: Contraction in sphincter muscles
- β_2: Relaxation of detrusor muscles

→ **Urine retention**

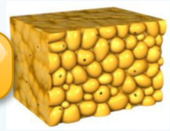
β_2:

- **Relaxation of bronchial muscles**
- **Bronchodilatation**

Metabolic effects



- β_2: **Glycogenolysis** — ⇑ glucose



- β_3: **Lipolysis** — ⇑ free fatty acids
- α_2: ⇓ insulin secretion
- ⇑ Metabolism → ⇑ O_2 consumption

Adrenocortical action

Eosinopenia due to

- Direct effect of adrenaline
- ⇑ ACTH (Adrenocorticotrophic hormone)
- ⇑ hydrocortisone release from adrenal cortex → eosinopenia

Antihistaminic and antiallergic effect

Adrenaline is the physiological antidote of histamine

Histamine acts on H_1 receptor → Bronchospasm
Adrenaline acts on β_2 receptor → Bronchodilatation

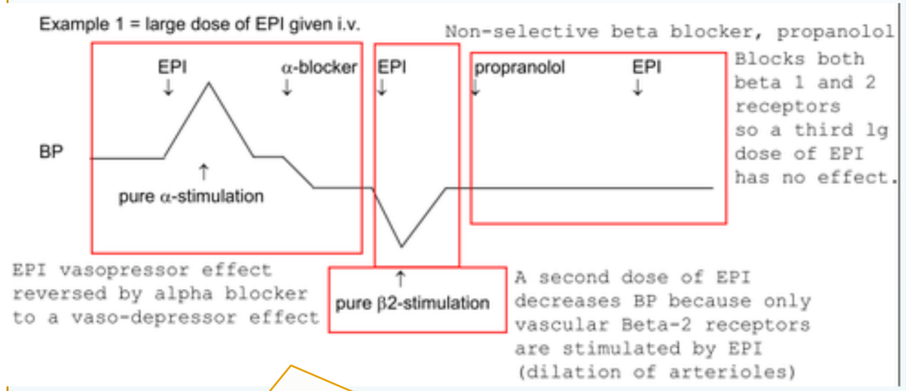
CNS

Have a weak stimulant effect

1- Adrenaline (Epinephrine) (AD)

- Synthesis ✓
- Termination of action ✓
- Absorption of adrenaline ✓
- Pharmacological actions ✓
- Adrenaline reversal !

Using anesthetized cat blood pressure



Non-selective beta blocker, propanolol

Blocks both beta 1 and 2 receptors so a third lg dose of EPI has no effect.

EPI vasopressor effect reversed by alpha blocker to a vaso-depressor effect

A second dose of EPI decreases BP because only vascular Beta-2 receptors are stimulated by EPI (dilation of arterioles)

Normally

NA acts on: $\alpha - \beta_1$ → causing hypertension
AD acts on: $\alpha - \beta_1 - \beta_2$ → causing hypertension

After using α blocker

NA → effect is abolished
AD → **"no α effect"**- β_1 - " β_2 → **Vasodilatation → hypotension "**
So, in the presence of α **blocker** AD causes hypotension as it acts only on β_2 receptors

Therapeutic uses of adrenaline

1. **Bronchodilators** in bronchial asthma and bronchitis
2. **Nasal decongestant**
3. AD is **used with local anesthetics** to delay absorption ,so prolong duration of action
4. **Allergy and hypersensitivity** → AD is used in case of anaphylactic shock (AD is a physiological antidote of histamine)
5. **Insulin hypoglycemia**
6. **Local hemostatic** → used topically to decrease oozing of capillary blood vessels (ex. nasal bleeding)
7. **Cardiac resuscitation** (AD may be injected intracardiac)
8. **Glaucoma**

Contraindications

1. **Hypertension** AD may lead to cerebral hemorrhage
2. **Coronary diseases** (coronary arteries gives the heart low amount of blood) → so it can not withstand the excess work produced by AD " ⇑ O_2 demand " → leading to anginal attacks
3. **Hyperthyroidism** → due to high production of adrenergic receptors on blood vessels
4. **General anesthesia** → as anesthetics potentiate the effect of AD on the heart leading to cardiac arrhythmia
5. **Patients receiving digitalis** (digitalized patients) as their hearts exert more work so AD would make their hearts exert more and more work !

2- Noradrenaline (Norepinephrine) (NA)

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Released from

1. NA is the neurotransmitter *released at postganglionic sympathetic nerves*
2. NA represents *20% of adrenal medulla secretions*

Routes of administration

ONLY by IV infusion
NOT given SC injection → as NA has a strong vasoconstriction effect that may lead to necrosis of skin and SC tissues
NOT given by IV injection may → cause cardiac arrest

Mechanism of action

NA stimulates
α receptors → **MAINLY**
β_1 receptors → **to lesser extent**
and has NO EFFECT on β_2 receptors

Effect of NA on CVS

1. **Blood vessels** → generalized vasoconstriction→α_1 effect and no β_2 effect
2. **Blood pressure** → increases systolic and diastolic
3. **Heart** → **a)** increase force of contraction (+ve inotropic effect)
   b) Reflex bradycardia ! (to compensate the vasoconstriction increasing blood pressure)

Therapeutic uses

Pressor agent
Used in controlling hypotention during spinal anesthesia

Simplified

Noradrenaline	Adrenaline	Isoprenaline
α β	**αβ**	α **β**

3- isoprenaline

Synthetic drug → isopropyl noradrenaline
Mainly metabolized by COMT and poorly by MAO

Mechanism of action

Non-selective β agonist directly →
stimulates β_1 and β_2 receptors
and has NO EFFECT on α receptors

Pharmacological actions

CVS β_1

1. increase heart rate **(+ve chronotropic)**
2. increase force of contraction **(+ve inotropic)**
3. increase cardiac output
4. **Blood pressure** → slight or no change (no vasoconstriction)

Smooth muscles β_2

1. Bronchodilatation
2. Decrease tone and motility of intestine and urinary bladder
3. Relaxation of human pregnant uterus

Therapeutic uses

1. Cardiac stimulant (in case of bradycardia)
2. Bronchodilator (rarely used in asthma "NON-SELECTIVE" → causes tachycardia and palpitations)

4. Dopamine

- **Dopamine is precursor for NA (as illustrated before)**
- **Dopamine** is synthesized and released from dopaminergic nerves
- It is also an important neurotransmitter **in CNS**

Types of dopamine receptors

- **D₁** → Peripheral receptors → its stimulation causes vasodilatation
- **D₂** → central receptors → responsible for the neurotransmitter function in CNS

Pharmacological actions

Dopamine can work also on α₁ and β₁ receptors

(D₁ > β₁ > α₁)

so, its action will differ according to the used concentration

Low dose

Stimulation of D₁ receptors in renal and mesentric blood vessels → vasodilatation → increase blood flow to kidneys and viscera

Moderate doses

Also stimulation of β₁ receptors in the heart → +ve inotropic effect (⇑ force of contraction)

High doses

Also stimulation of α₁ receptors → Vasoconstriction and **indirect effect** → NA release from nerve terminals

Therapeutic uses

1. Cardiogenic shock (shock causes heart to stop)
As dopamine stimulate β₁ receptors → +ve inotropic and **D₁** receptors → increase renal blood flow → so avoid renal shut down
2. Chronic refractory congestive heart failure
3. Hypovolaemic shock
4. Can be used in kidney failure (renal vasodilatation)

5. Dobutamine

- **Dopamine analogue**
- Dobutamine **does not act on dopaminergic** receptors !!
- Dobutamine is a **selective β₁ agonist**
its inotropic effect is > Chronotropic effect

# AD , NA , Dopamine → Natural
# isoprenaline , Dobutamine → Synthetic

Therapeutic uses

Used in congestive heart failure → improve myocardial function with minimal change in heart rate → which is an advantage of dobutamine over other sympathomimetics → *less O₂ demand*

II. Non catecholamines

1. Ephedrine

1. Natural alkaloid obtained from Ephedra plants and can be prepared synthetically
2. Resistant to MAO and COMT *(as it is non catecholamine)* so, it has **long duration of action**
3. Effective orally
4. It is a tertiary alkaloid Lipid soluble so, it can cross BBB so, it has **CNS stimulant effect**

Mechanism of action

Dual (mixid) action

1. Direct
Stimulation of adrenergic receptors → both α and β receptors

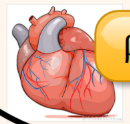
2. indirect (main action)
increase NA release from sympathetic nerve terminals → then NA act on both α and β₁ receptors

Repeated administration of Ephedrine produces tachyphylaxis *(decreased response on repeated administration)* → due to ***depletion of NA stores***

Pharmacological actions

Similar to adrenaline !

CVS



+ve inotropic and +ve chronotropic effects

Vasoconstriction of blood vessels

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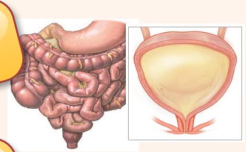
⇑ blood pressure → **slower effect** than AD as it acts indirectly but **more prolonged action**

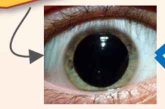
Smooth muscles



Relaxation of GIT and urinary bladder

Eye

Active mydriasis (ACTIVE → as it affects the radial muscles of iris α₁ which is responsible for mydriasis)



No effect on "accomodation for near vision" and "light reflex"

CNS

Alertness , Anxiety , insomnia

Skeletal muscles

Facilitates neuromuscular transmission (antifatigue effect)

Therapeutic uses

1. Prophylactic in bronchial asthma
Not used in acute attacks of asthma → as it has delayed onset of action *(because of its indirect effect)*
2. Nasal decongestant
3. Pressor agent in spinal anesthesia (to reverse hypotension)
4. Mydriatic
5. Narcolepsy مرض النوم المفاجئ
6. Anorexigenic (appetite suppressant)

Side effects

1. insomnia (abused for this action → more studying at night !)
2. Urine retention in elderly patients with enlarged prostate
3. Tachyphylaxis

2. Amphetamine

- Synthetic indirectly acting sympathomimetic
- Rapidly absorbed from GIT
- Not hydrolysed by MAO or COMT
- Can cross BBB so, it is a **potent CNS stimulant**
- **produces tolerance**

Mechanism of action

indirectly acting
increase NA release from sympathetic nerve terminals

Pharmacological actions

1. Psychic stimulation (euphoria - increases mental and physical activities)
2. Analeptic (increase alertness)
3. Antifatigue action (abused by athletes to give extra power !)
4. Anorexigenic (appetite suppressant)
5. Mild analgesic action
6. Tolerance and development of addiction

Therapeutic uses

1. Attention deficit hyperactivity disorder ADHD in children
→ Here the child suffers from lack of giving attention at any activity, hyperkinetic (hyper mobility / hyperactive) , nervousness .. etc
→ Amphetamine can manage this case paradoxically (illogically) (paradoxical effect)

2. Narcolepsy مرض النوم المفاجئ

Selective adrenergic agonists

Selective α_1 agonists

Phenylephrine
Methoxamine

Direct stimulants to α_1 receptors
→ so produces vasoconstriction and mydriasis

Therapeutic uses

1. Nasal decongestant (Afrin®)
2. Mydriatics
3. Pressor agents in spinal anesthesia
4. Local vasoconstrictor with local anesthetics (to reduce systemic absorption and prolong the action)

Selective α_2 agonists

Clonidine (Catapress®) (rarely used now due to its side effects)
Methyldopa (Aldomet®)

Stimulants presynaptic α_2 receptors
→ Decreases NA release

Therapeutic uses

Treatment of hypertension

Selective β_2 agonists

Salbutamol (Ventolin®)
Terbutaline

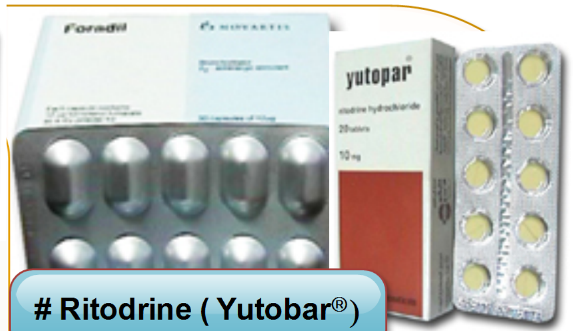
It can be used orally or by inhalation (to give a
→ **stimulates** β_2 receptors in bronchi → produces bronchodilatation

Therapeutic uses

Treatment of **acute attacks** of bronchial asthma

....

# Formeterol & Salmeterol → Long-acting β_2-agonist
→ used in management of asthma but not in acute attacks



Ritodrine (Yutobar®)

Selective β_2 agonist → used as a myometrial relaxant (relax the uterus) during pregnancy
So, can be used in **premature labour**

4- Sympatholytics

I. α adrenergic blockers

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a) Non selective α blockers

- They produce vasodilatation → hypotension
- They **reverse** the pressor effect of **AD** → **(Adrenaline reversal)**
- They **abolish** the pressor effect if **NA**

1. Ergot alkaloids

a- Ergotoxine

- **α blocker** → vasodilatation → decrease blood pressure

Therapeutic uses

1. Hypertension
2. Cerebral ischemia (to increase cerebral blood flow)
3. Raynaud's disease (peripheral vascular disease)

# Dihydroergotoxin is a potent α blocker

Other ergot alkaloids have no α blocking effect but let's talk short notes about them

b- Ergotamine

- **Potent and direct vasoconstrictor but weak α blocker**

Therapeutic uses

Used to treat migraine attacks (by inducing vasoconstriction of cranial blood vessels → reverse the cranial vasodilatation of migraine headache)
# Cafergot → ergotamine + Caffine → Synergestic effect
→ used for treatment of migrane

c- Ergometrine

- **Oxytocic → potent stimulation of uterine muscles**
→ **increase contraction of uterus**

Therapeutic uses

Used in obstetrics 1. induction of labour
2. prevent postpartum haemorrhage

# Methylergometrine is a powerful oxytocic

2. Phenoxybenzamine

Potent non selective α blocker (block both α_1 and α_2)

Mechanism of action

1. **irreversible** competitive antagonist (covalent binding) at α receptors
2. Slow onset and long duration of action (3 - 4 days)
3. Antihistaminic , antiserotonin (5HT) and anticholinergic actions

Therapeutic uses

1. Raynaud's disease (vasocontriction in peripheral vascular diseases)
2. Pheochromocytoma

Side effects

1. Postural / orthostatic hypotension
2. Reflex tachycardia
3. Failure of ejaculation

3. Phentolamine & Tolazoline

Potent non selective α blocker (block both α_1 and α_2)

Mechanism of action

Reversible competitive antagonist at α receptors

Therapeutic uses

1. Raynaud's disease
2. Pheochromocytoma
3. Frostbite

# Tachycardia produced by non selective α blockers (Phentolamine and Phenoxybenzamine) happens due to

1. **Reflex tachycardia** → baroreceptors (receptors sensitive to blood pressure) → when it detect hypotension → it induces reflex tachycardia (⇑ heart rate) to increase blood pressure again
2. **Blocking $\alpha 2$ receptors** → increase NA release → sympathetic stimulation of the heart → tachycardia

b) Selective α blockers

1. Selective α_1 blockers

- Prazosin
- Terazosin
- Doxazosin

They block α_1 receptors with no effect on α_2 receptors
→ They cause vasodilatation so decrease blood pressure
They cause very little tachycardia as they have no effect on α_2 receptors

Therapeutic uses

1. Hypertension
2. Benign prostatic hyperplesia (act by blocking α_1 receptors in bladder neck sphincter → relaxation of sphincter muscle → improve urine outflow

Other selective α_1 blockers

1. Tamsulosin

Highly selective to block α_{1A} receptors rather than α_{1B} receptors
→ so, used mainly in treatment of benign prostateic hyperplasia (BPH)

# Types of α_1 receptors

a. α_{1A} receptors → found in the sphincter of urinary bladder
b. α_{1B} receptors → in blood vessels

2. indoramin

α_1 blocker *with direct myocardial suppressant action* → **so, no reflex tachycardia**

2. Selective α_2 blockers

Yohimbine

→ increase NA release from sympathetic nerve terminals

Therapeutic uses

1. **Aphrodisiac** (treatment of male sexual dysfunction and impotence) (not used now)
2. Experimental tool

4- Sympatholytics

I. α adrenergic blockers ✓

II. β adrenergic blockers

1. Non selective β blocker block both β_1 and β_2

With ISA
Pindolol
Oxyprenolol

no ISA
Propranolol
Nadolol

2. Cardioselective selective β_1 blocker

With ISA
Acebutalol

no ISA
Atenolol

3. Selective β_2 blocker

Butoxamine
used as an experimental tool

# ISA (intrinsic sympathomimetic activity) → partial agonist so, they will not produce severe bradycardia

# Non-selective β blockers can not be used in asthmatic patients as they block β_2 receptors which are responsible for bronchodilatation !

Cardioselective β_1 blockers and also β blockers with ISA can be used in asthmatic patients

Drugs blocking both α and β receptors

Labetalol
1. Decrease cardiac output (CO) → β blocking effect
2. Decrease peripheral vascular resistance due to → α blocking effect (vasodilatation)
it has rapid onset of action and used in treatment of hypertension

Propranolol

1. Pharmacokinetics

- Completely absorbed from GIT
- Metabolized in liver
- Excreted in urine
- Half-life $t_{1/2}$ = 3 - 10 hrs for most β blockers

2. Mechanism

- Non selective β blockers without ISA
- Has membrane stabilizing action (local anesthetic - quinidine like action)

3. Pharmacological actions

CVS

1. Bradycardia
2. ⇓ force of contraction
3. ⇓ Cardiac output (C.O)
4. Antiarrythmic action (quinidine like action)
5. ⇓ Blood pressure due to
   a) ⇓ C.O
   b) ⇓ Renin release → ⇓ angiotensin → ⇓ vasoconstriction *(renin is released from juxtaglomerular cells through β_1 stimulation)*

Bronchi

Bronchoconstriction / Bronchospasm due to blocking of β_2 receptors in bronchi

Metabolic

Blocking β_2 receptors in liver inhibit glycogenolysis

4. Therapeutic uses

1. Cardiac arrhythmia (⇓ heart rate)
2. Prophylactic (prevention) against anginal attacks → ⇓ cardiac work so ⇓ O_2 demand
3. ⇓ Prophylaxis against myocardial infarction (prevent arrhythmia in patients with MI)
4. Hypertension (delayed response)
5. Glaucoma (by blocking β_2 receptors in ciliary body leading to ⇓ secretion of aqueous humor so ⇓ IOP (**Timolol is prefered in treatment of glaucoma)**
6. Prophylactic against migraine
7. Hyperthyroidism / Thyrotoxicosis / Thyroid storm → used preoperatively to protect against tachycardia
8. Pheochromocytoma .. combined with α blocker before surgery
9. Anxiety states as palpitation and tremors associated with sympathetic overactivity such as stage fright

5. Side effects

1. Severe bradycardia and hypotension
2. Heart failure in case of inadequate mycardial function
3. Bronchospasm
4. Augments (strenghthen) hypoglycemic effect of insulin (⇓ glycogenolysis) in diabetic patients + β blocking masks hypoglycemic alarms (tachycardia - tremors - anxiety)
5. Fatigue - dizziness - muscle aches
6. Night mares
7. Allergic reactions
8. Cold hands

6. Contraindications

1. Congestive heart failure
2. Bronchial asthma
3. Partial heart block

4- Sympatholytics

I. α adrenergic blockers ✓

II. β adrenergic blockers ✓

III. Adrenergic neuron blockers

They act by inhibition of

Release of Noradrenaline
Guanethidine

Storage of Noradrenaline
Reserpine

Synthesis of Noradrenaline
α methyldopa

Ph. Alaa Nasr

1. Guanethidine

Mechanism of action

1. inhibit NA release
2. inhibit NA uptake

Pharmacological actions

1. Decrease blood pressure
2. Does not antagonize exogenous catecholamines but it potentiates them

Therapeutic uses

1. Hypertension
2. Glaucoma

Side effects

1. Postural / orthostatic hypotension
2. impotence (failure of ejaculation)
3. Diarrhea
4. Nasal congestion

2. Reserpine

Mechanism of action

1. inhibits granular uptake (storage) of NA so, MAO can rapidly metabolize it in the cytoplasm that leads to depletion of NA
2. Reserpine causes depletion of stores of catecholamines and serotonin centrally (in brain) and peripherally (in organs)

Pharmacological actions

1. **Centrally:** ⇓ NA in brain leads to sedation and tranquilizing actions
2. **Peripherally:** Hypotension

Therapeutic uses

1. Hypertension
2. Psychotic states

NOVARTIS
Brinerdin
30 tablets

Side effects

1. Postural / orthostatic hypotension
2. Mental depression and suicidal attempts
3. Sedation
4. Nightmares

HYPOTEN
ANTIHYPERTENSIVE

3. Alpha methyl dopa

Mechanism of action

1. inhibition of DOPA decarboxylase enzyme so prevent synthesis of NA → and produces α**-methylnoradrenaline** which is a false transmitter stored at the nerve ending instead of NA

2. α**-methylnoradrenaline** stimulates α_2 receptors in the brain → leading to decrease NA release and decrease sympathetic tone

Therapeutic uses

Hypertension
*(Methyldopa is **safe** during pregnancy)*